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THE INFLUENCE OF RESPIRATION ON VENOUS PRESSURE

By OVID O MEYER and WILLIAM S MIDDLETON

(*From the Department of Medicine University of Wisconsin*)

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The effects of the respiratory movements upon the circulation have seriously concerned physiologists and clinicians for many years The classical experiments of Poiseuille (1) constitute the first substantial contribution to the knowledge of the influence of respiration upon the venous flow The following quotations state his conclusions

Ainsi, au moment de l inspiration, l air de la poitrine se raréfiant par la dilatation de cette cavité, la pression de l atmosphere l'emporte sur celle de l'air qui y est renfermé et le sang des veines jugulaires tend à se précipiter dans le thorax, au contraire, dans l'expiration, la poitrine se resserrant, la pression de l'air intérieur devient plus grande, les veines sont comprimées, par suite le sang de ces vaisseaux reflue hors de la poitrine

Ainsi, nous croyons devoir conclure qui si l'inspiration appelle vers la poitrine une certaine quantité de sang veineux l'expiration aussi concourt puissamment à mouvoir le sang vers le coeur

Nous concluons que l aspiration due à la dilatation de la poitrine et à celle du côté droit du coeur n est point la cause principale du mouvement du sang veineux mais que par cette aspiration les gros troncs veineux se déchargeant dans la poitrine, le sang veineux des autres veines trouve seulement moins de résistance à se mouvoir, cette cause n'est donc qu'accessoire et rien de plus.

A considerable literature has grown about this subject, but no worker has carried his studies to more exact conclusions than Poiseuille. One of his most important observations was the increase in the respiratory influence on the venous pressure as the thorax is approached Burton Opitz (2) by improved methods established a decrease in venous pressure from the periphery to the center of the circulation at the rate of 1 mm of mercury for each 35 mm distance Negative pressure was first noted by him in the veins in close proximity to the

thoracic cavity, and variations in the venous pressure dependent upon the respiratory movements were most marked here The lowest pressures were recorded at the end of inspiration and the highest at the end of expiration Burton-Opitz established a disappearance of the negative venous pressure even in the veins abutting the thoracic cavity, when the negative intrapleural pressure was relieved by a pneumothorax By electropolygraphic methods Waud (3) noted the rise of the venous curve in the latter half of inspiration and its continuance into the beginning of expiration The period of inertia into the expiratory phase constituted about two cardiac cycles

Most authorities are apparently agreed on the minor influence of the respiratory activity on the venous pressure in the small peripheral veins of normal individuals Sewall (4) remarked that "the superficial veins of the extremities normally dilate and the pressure within them increases as result of inspiration The respiratory movements of the veins correspond with the respiratory changes in arterial blood pressure" This phenomenon he attributed to the increased flow from the capillary bed, but ample evidence (5) (6) is available to disprove a direct relationship between either capillary or arterial blood pressure and venous pressure Furthermore, Gottwald (7) adduced evidence that the venous pressure changes of respiration are independent of circulatory acceleration and apparently entirely dependent upon changes in the intrapleural negative pressure Bedford and Wright (8), by the direct method of Claude, found no influence on the venous pressure (in the arm veins) of nor nal individuals on ordinary breathing One-half to one cm of water variation was determined in certain pathologic cases

Some difference of opinion exists in the question of the comparative figures for venous pressure changes in the upper and the lower extremities under the influence of respiration Since the present studies deal only with venous pressure in the arm, the merits of the two sides of the question need not be discussed

Disturbances of the respiratory rhythm reflect themselves very promptly in venous pressure changes Bedford and Wright (8) recorded invariable rises in the venous pressure on holding a deep breath, for example, a normal pressure of 7 cm of water rose to 25 cm Conversely they noted falling venous pressures on over-ventilation

In the headdown position Henderson, Prince and Haggard (9) established a fall of from 8 to 11 cm of venous pressure in six normal subjects on voluntary hyperpnoea, the values reaching the negative level They attributed this fall to the decreased carbon dioxide content of the blood In their opinion, carbon dioxide is an active veno pressor agent. Kroetz (10), likewise, corroborated the constant fall in venous pressure on over-ventilation His figures 0 7 to 2.5 cm , represent the slightest decrease recorded and he furthermore noted that this fall occurred within the first 20 seconds of the exercise

These physiologic observations of the influence of respiration upon the venous pressure suggest many points of clinical application Occasion (5) has been taken to report the virtual pathognomonic value of venous pressure readings in cardiac decompensation and the conclusion has been drawn that "excluding local causes of venous obstruction, abnormal venous pressures invariably mean cardiac failure, independent of the cause of failure or the associated disease " Added experience in the study of the venous pressure in respiratory diseases of the nature of lobar pneumonia confirms the conclusion above drawn Contrary to Kroetz's experience (10) bronchial asthma per se in the interval between attacks induced no elevation of the venous pressure in a series of 11 cases, 8 of whom were emphysematous An additional group of 5 cases of emphysema fro n causes other than bronchial asthma likewise failed to exceed the normal limit of 11 cm of water venous pressure The figures for this group ranged from 5 to 11 cm. of water During the asthmatic seizures the venous pressure rises precipitously and is maintained at high levels, as witnesses a case of this series in whom the venous pressure mounted from 11 to 23 cm of water during a severe attack which lasted 2½ hours An extreme case of pneumoconiosis, terminating fatally, showed venous pressure readings between 14 and 16 cm of water, and at necropsy presented a clear picture of right heart failure succeeding compensatory right sided hypertrophy Four cases of pneumoconiosis without signs of myocardial involvement showed no rise of venous pressure

Turning to disturbances of the respiratory rhythm the possible influence of Cheyne Stokes' respiration on the venous pressure suggested itself Burger (11) has shown plethysmographic changes of a rhythmic order in Cheyne Stokes' respiration Accordingly venous pres

sure changes might be anticipated Twenty-two observations have been made on 18 patients with this disturbance of the respiratory rhythm The elevation of the venous pressure during the apnoeic period has been invariable, as has also been the fall from this high level during the succeeding hyperpnoea The average difference in the venous pressure readings of the apnoeic and the hypernoeic periods was 6 cm of water in this group of cases The greatest fluctuation occurred in a cardio-renal patient, whose venous pressure registered 28 cm of water in apnoea and 16 cm in the hyperpnoeic period While the duration of the apnoea and the degree of hyperpnoea apparently exerted considerable influence in determining the variations in a given individual, it is important to note that no rule could be formulated for an average response under similar conditions in a second subect

Significant changes in the venous pressure likewise occur under the conditions of general anaesthesia Meyer and Middleton (12) have collected data establishing a virtually constant rise of venous pressure during induction, which they attribute to the disturbed respiratory rhythm, muscular effort and possibly an elevated carbon dioxide content of the blood Thereafter the venous pressure falls to a plateau, usually somewhat above the normal for the subject, and maintains this level, except for periods of muscular activity or altered respiration, throughout the anaesthesia

Certain physiologic acts, as defecation, parturition, coitus, coughing, and lifting, or occupations, as glass-blowing, playing wind instruments and the like, constitute an interesting problem from the circulatory standpoint The following episode is not unusual

E H , a white male, 64 years of age, laborer by occupation, was admitted to the Bradley Memorial Hospital on December 7, 1920, complaining of shortness of breath Precordial distress had developed on effort about a year previously and succeeding this experience dyspnoea became increasingly evident on slight strain About six months after the onset, oedema appeared in the extremities and later the abdomen bloated

The past medical history offered scarlet fever as the only suggestive etiologic background The occupation of laborer had been changed to painter within the past 4½ years Otherwise the social and family histories were irrelevant

Physical examination established the existence of marked cardiac decompensation with emphysema, pulmonary oedema, relative mitral insufficiency, and general arteriosclerosis Under bed rest and digitalis therapy the passive congestion

of the lungs, general anasarca and subjective condition of the patient improved for a time, but on the 31st day after admission the venous pressure which had gradually advanced from 6 cm of water to 11 cm , sharply rose to 20 cm. Coincidently the oedema of the lungs increased and the liver was palpable 5 cm below the costal margin in the right midclavicular line The patient became cyanotic and dyspnoea was profound Accordingly 400 cc of blood was let and the venous pressure fell to 5 cm with corresponding improvement in the subjective and objective evidences of right heart failure Within the next two days the venous pressure had stabilized at 8 cm and the general and circulatory conditions were satisfactory

Thereafter the circulatory balance fluctuated and the venous pressure ranged from 8 to 16 cm However, on the 8th day after venesection the venous pressure was read at 8 cm and there were fewer basal râles In the afternoon the patient was helped to a commode had an evacuation of the bowels and fell to the floor dead

So called "bed pan" deaths are relatively common occurrences in large general hospitals dealing with great numbers of cardio vascular cases In effect, the effort represented by defecation and the other circumstances listed constitutes a Valsalva experiment, a forced expiratory effort with the glottis closed Dawson and Hodges (13) have thoroughly analyzed the situation from the standpoint of the arterial hemodynamics Moritz and v Tabora (14) and Burger (11) have recorded marked rises in the venous pressure under the Valsalva experiment to 42 cm and 50 cm of water respectively Kroetz (10) similarly obtained a figure of 40 cm Mosler and Balsamoff (15) made extensive observations on this phenomenon and suggested its use as a measure of cardiac tonus They voiced the obvious necessity of avoiding such strain, when possible, in the cardiac cripple On the other hand, Schott (16) suggested measurements of the venous pressure under the circumstance of a static effort, raising the leg, as a guide to the circulatory efficiency He established a definite parallelism between the venous pressure curve and the ability of the heart to meet this static test If this were true, it seemed even more logical to employ a dynamic test to establish the myocardial integrity

First of all in order to standardize the procedure the indirect method of Hooker and Eyster (17) for the venous pressure determinations was routinely applied to subjects in the recumbent position The subject was carefully instructed in the technique and the design of the Valsalva test, being particularly cautioned after taking a deep inspiration to

exert as great an expiratory effort for as long a period as possible One hundred and two tests were made on 51 normal subjects The readings were taken at as frequent intervals as possible during the period of strain, and an assistant with a stop-watch recorded the time of these observations The results were constant in the steady advance of the venous pressure through the period of effort The curve

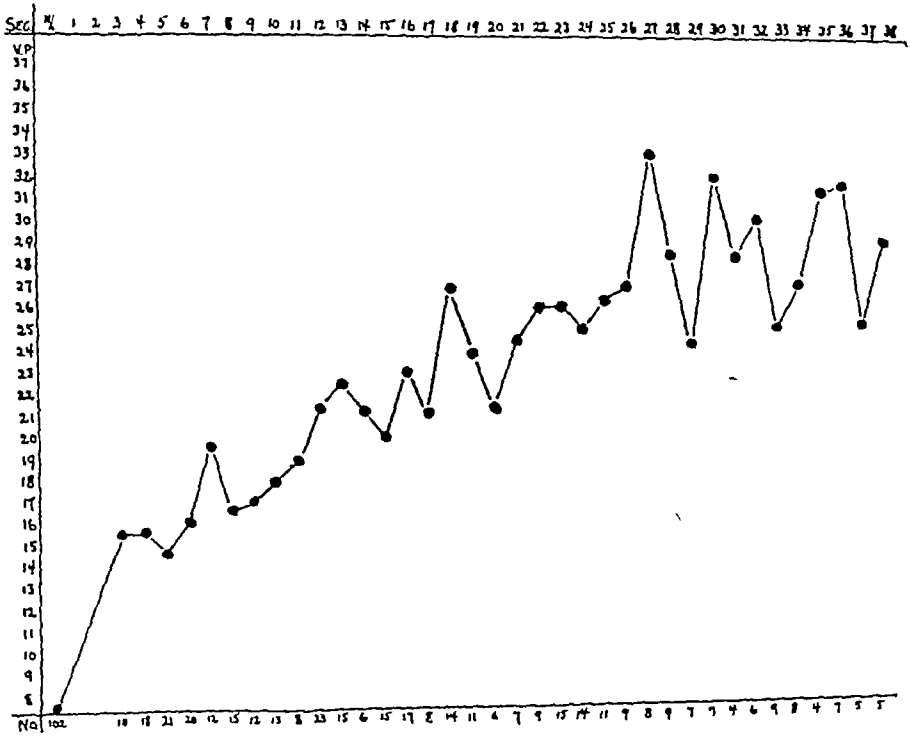

FIG 1 MEAN CURVE OF VENOUS PRESSURE RESPONSE OF 51 NORMAL SUBJECTS TO THE VALSALVA EXPERIMENT

(No indicates observations made at various time intervals)

(fig 1) of the mean pressure for the several seconds is misleading in indicating fluctuations, but the general upward tendency to the twenty-eighth second will convey a fair impression of the curve of the average individual After this period the number of subjects and their wide variance in pressure levels render the mean curve useless It will be noted that the greatest single increment or percentage rise

is in the first three seconds of the Valsalva In figure 2 a single normal individual has been selected at random and the curve of his venous pressure response to the Valsalva experiment plotted against the averages (of figure 1) for the same time intervals A close coincidence of the curves will be remarked up to 27 seconds when the two diverge

Naturally there is a wide individual variation in the duration and

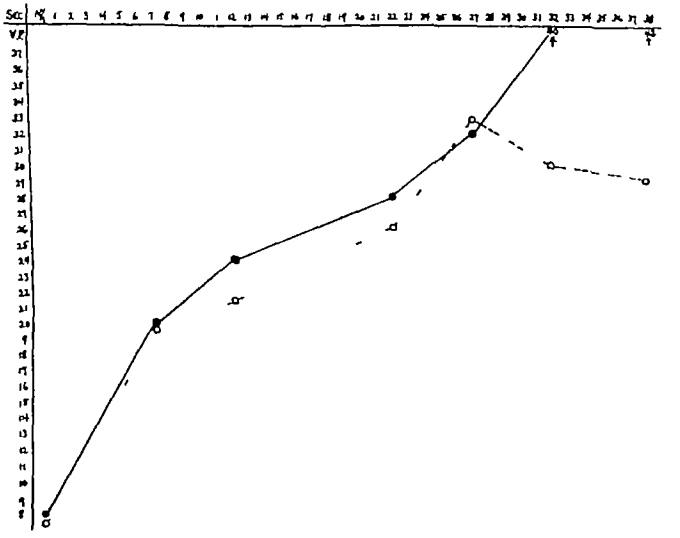

FIG 2 CURVE OF VENOUS PRESSURE RESPONSE OF A SINGLE NORMAL SUBJECT TO THE VALSALVA EXPERIMENT (SOLID LINE) AS COMPARED WITH NORMAL MEAN (BROKEN LINE)

the force of the expiratory effort Failure of the subject to maintain the expiratory effort (or 'leak' as it came to be termed) is readily detected in the failure of the venous pressure curve to continue its rise However, 48 of the 51 normal controls continued the effort for over 20 seconds The majority of the group (31) maintained the expiratory effort for from 20 to 35 seconds and 17 exceeded 35 seconds From a normal level of 7 6 cm of water only 4 individuals failed to exceed a

venous pressure of 20 cm of water in their forced expiratory effort The great majority (44) ranged between 20 and 40 cm venous pressure at the height of their effort and 3 exceeded 45 cm One of this high group of 3 responded unusually in levels of 50, 52, 50 and 52 cm

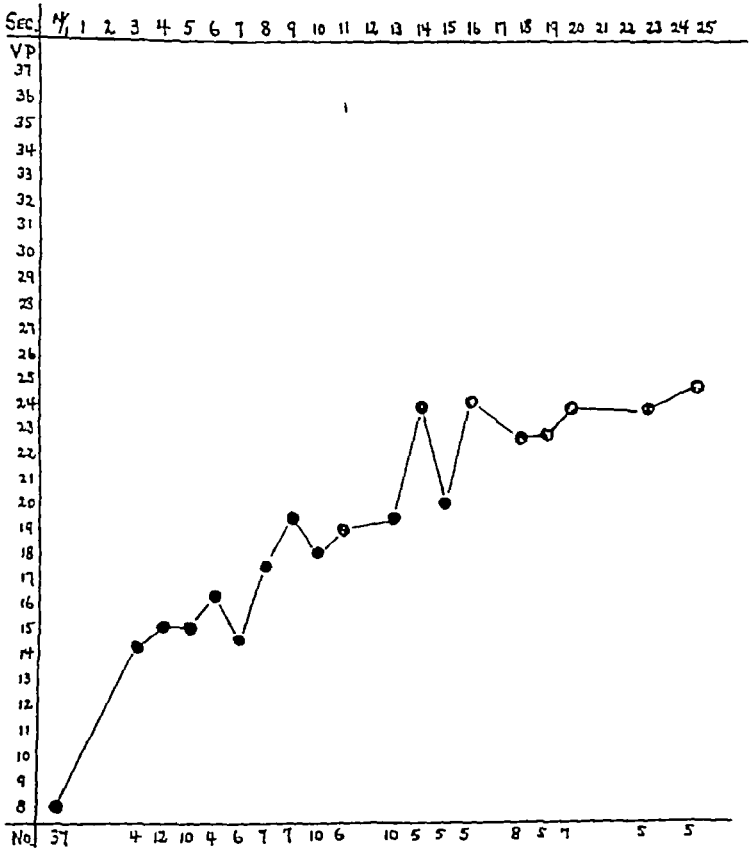

FIG 3 MEAN CURVE OF VENOUS PRESSURE RESPONSE OF 31 NORMAL SUBJECTS TO MÜLLER EXPERIMENT

(No indicates observations made at various time intervals)

of water venous pressure, respectively, on each of four successive trials, maintaining the effort for 18, 28, 24 and 26 seconds for the corresponding tests An intervening rest of 2–3 minutes elapsed between the several tests Only one other normal individual approximated this level (50 cm of water after 30 seconds of the Valsalva test)

Repetition of this expiratory effort apparently developed an increased capacity in certain individuals, in that of 51 repeated observations 3 exceeded 55 seconds of strain However, the figures for the remaining time intervals are comparable between single and repeated trials Again the majority of the tests (45) showed a response of venous pressure to between 20 and 40 cm of water Four Valsalva responses ranged from 40 to 52 cm , including the three figures given in the last paragraph as repeated observations on an individual whose first reaction was high While the data stated do not confirm the impression, it is felt that, as a rule, repetition of the Valsalva effort at short intervals tends to cause increasingly higher response curves of venous pressure in a given individual

The Müller experiment of a resisted inspiratory effort with the chest in the expiratory position was investigated with relation to its influence upon the venous pressure Burger (11) and Kroetz (10) reported a constant fall to 4–5 cm and 2 5 cm of water, respectively Thirty seven observations were made on 31 individuals and the resultant mean curve (fig 3) has been plotted from the figures for the several seconds The greatest increment of increase in venous pressure occurs in the first 3 seconds as in the Valsalva experiment Neither the primary rise nor the ultimate peak is as high as in the Valsalva Without exception the individual curves show a constant upward tendency, and again seem dependent in a measure upon the duration and the force of the effort The highest venous pressure of 50 cm of water was recorded after 24 seconds of effort and significantly he was the same subject in whom four unusually high responses to the Valsalva were noted above No explanation has been found for the discrepancy between these results and those reported by Burger and Kroetz, and it is merely affirmed that, in the present studies, venous pressure readings were made from the time of initiation of the inspiratory effort with the chest in the expiratory position In no instance was there determined a fall in the venous pressure during the continuance of the effort

Since the venous pressure serves as a measure of right heart load (5), the estimation of the myocardial reserve through some dynamic test such as the Valsalva or the Müller seemed feasible These tests of strain took precedence over the static tests such as utilized by

Schott (16) by reason of the difference in the load represented and accordingly the greater venous pressure responses to be anticipated therefrom At the same time the dynamic tests have the obvious disadvantage of a greater individual variation in the effort expended The Valsalva experiment was used in preference to the Muller, be-

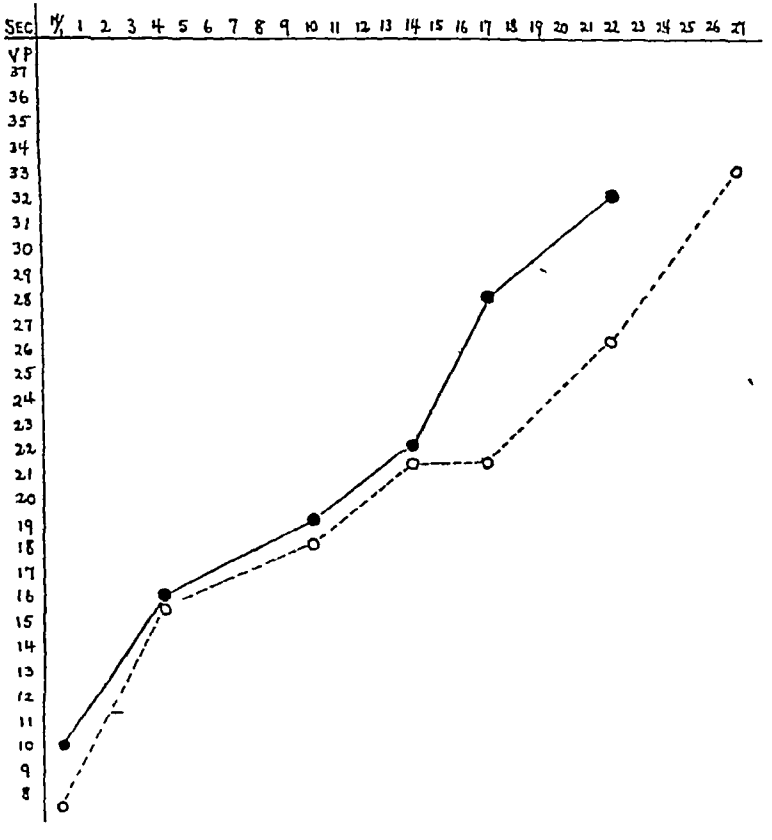

FIG 4 CURVE OF VENOUS PRESSURE RESPONSE TO VALSALVA EXPERIMENT IN FULLY COMPENSATED HYPERTENSIVE PATIENT (SOLID LINE) AS COMPARED WITH NORMAL MEAN (BROKEN LINE)

cause it is a more natural procedure Instruction is simple and for a given normal individual the response within reasonable limits is relatively constant

The realization of the strain implied in the test led to the greatest care in the choice of cardio-vascular subjects At first only completely

compensated cases were studied, and their response as typified by figure 4, taken from a hypertensive subject with cardiac hypertrophy, coincides closely with the normal mean On the other hand two types of response occurred where evidences of myocardial insufficiency were slight but apparent In the first, as characterized by figure 5,

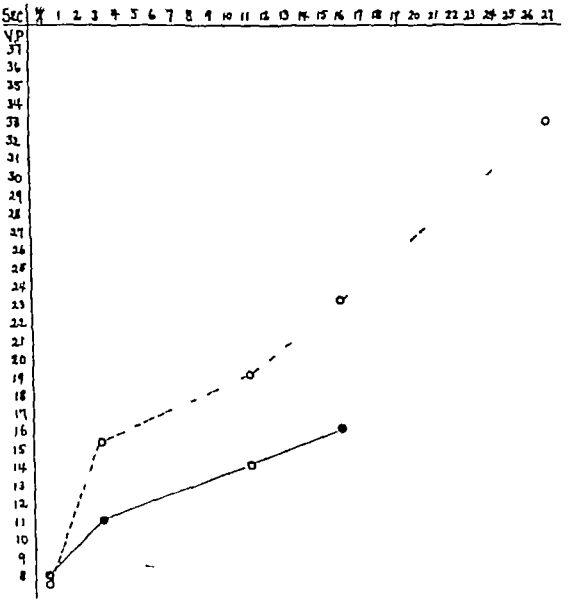

FIG 5 CURVE OF VENOUS PRESSURE RESPONSE TO VALSALVA EXPERIMENT IN PARTIALLY COMPENSATED CARDIAC PATIENT (SOLID LINE) AS COMPARED WITH NORMAL MEAN (BROKEN LINE)

there resulted a very inadequate response to the effort which was maintained for a very short period In figure 6 there is represented the response in an individual, whose basic venous pressure before the test was constantly elevated, and who showed other evidences of right heart inadequacy Under the Valsalva the venous pressure rise was

prompt but not comparable in degree to the normal primary response and the levels for the period of strain were above the corresponding means However, the effort was continued for a much shorter period than the average It may be hypothesized that nature protects such individuals against right heart strain of this order by limiting the time over which the effort may be sustained

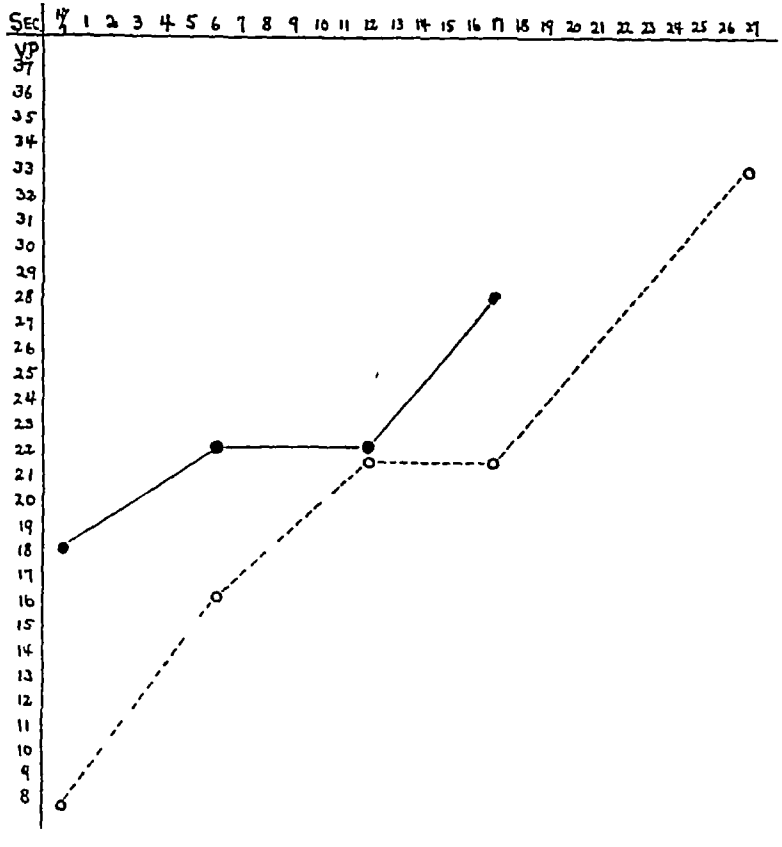

FIG 6 CURVE OF VENOUS PRESSURE RESPONSE IN PARTIALLY COMPENSATED CARDIAC PATIENT (SOLID LINE) AS COMPARED WITH NORMAL MEAN (BROKEN LINE)—VALSALVA TEST

CONCLUSIONS

1. The respiratory influence on the venous pressure is considerable and reflects itself in certain clinical conditions

2 Marked venous hypertension is noted during attacks of bronchial asthma, but in the interval between the attacks the venous pressure is unaltered, provided the myocardium be intact

3 Venous pressure is elevated in the apnoeic period of Cheyne-Stokes' respiration and falls during the hyperpnoea, regardless of the basic level of the venous pressure

4 Anaesthesia is attended by significant rises of venous pressure during induction and by a fall to a plateau somewhat elevated above the normal for the subject through the anaesthetic period

5 Great rises in venous pressure are found during the performance of the Müller and the Valsalva experiments These changes may contribute to the fatalities in cardio vascular patients under effort such as defecation, parturition and the like, which closely approximate the conditions of the Valsalva test

6 As a test of right heart efficiency such methods must have a very limited field of usefulness on account of the too serious risk involved It is possible that the venous pressure responses to the Valsalva test may give some prognostic information in the borderline case or some idea of the return of myocardial efficiency in the case followed through convalescence from a period of decompensation

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VENOUS PRESSURE IN GENERAL ANESTHESIA

By OVID O MEYER AND WILLIAM S. MIDDLETON

(From the Department of Medicine University of Wisconsin)

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Circulatory failure under general anesthesia has constituted a serious problem in medicine from the time of the introduction of chemical agents for this purpose With a measure of laboratory support in the demonstration of the paralytic action of chloroform on heart muscle by Embley (1), acute dilatation of the heart came to occupy an unquestioned position of predominance in explanation of circulatory collapse under general anesthetics of whatever order Scant clinical attention was granted the contribution of Levy (2) who demonstrated the increased irritability of the mammalian heart under light chloroform anesthesia and its reduction under deep anesthesia Abnormal ventricular beats were observed to arise under light anesthesia and the occurrence of ventricular fibrillation as an outgrowth of this circumstance led Levy to the conclusion that this disturbance of rhythm was probably the only important circulatory cause of death under chloroform anesthesia

Notwithstanding the sound basis of Levy's observation, cardiac dilatation remained the uncritical clinical diagnosis in the circulatory failure of general anesthesia until Levine (3) (4) directed attention to the gross disturbance of cardiac rhythm attendant upon such occurrences Paroxysmal auricular tachycardia, auricular fibrillation and paroxysmal auricular flutter were the profound arrhythmias of auricular origin noted by him in cases presenting the features of so-called cardiac dilatation during or succeeding operation

The situation with relation to the direct action of the several anesthetic agents on the heart muscle resolves itself into an unanimity of opinion as to the particular risk attaching to the exhibition of chloroform, since its level of toxic action on the myocardium is very

unusual effort effected pronounced rise of the venous pressure in the apnoeic period of Cheyne-Stokes' respiration and fall during the succeeding hyperpnoea The latter observation coincides with the fall of venous pressure noted by Henderson, Prince and Haggard (13) and by Kroetz (12) on voluntary hyperpnoea

Since the venous pressure reflects so distinctly, even in normal individuals, alterations in the force and the rhythm of respiration, pronounced changes in the venous pressure might be anticipated under the conditions of general anesthesia without thought of a primary circulatory responsibility for the same The earlier division of general anesthesia into three stages has given way to the modern classification of Guedel (14) (15), in which the third stage is subdivided into four logical strata according to well defined signs With the advent of improved methods of induction through the use of nitrous oxide preparatory to ether or ethylene administration Waters (16) divides the anesthesia into two periods, induction and maintenance Clearly the subject in Waters' classification passes quickly through the stage of induction, which includes the older first two stages, to the maintenance or former third stage, wherein the level of anesthesia is established by the condition of the subject and the operative demands of the surgeon

In the stage of induction the earliest effect of the anesthetic agent on the respiration may be to increase both rate and depth slightly It has been stated that with "modern skilled anesthesia, the second stage is usually passed with little or none of the external manifestations of excitement" (15) Commonly, however, there may occur either extreme of hyperpnoea or of breath-holding Physical effort may further complicate the picture from the standpoint of hemodynamics On a maintenance level the respirations are quieter, more regular, and more shallow in the first stratum of the third stage whereas respiratory depression does not appear until the fourth stratum (of the third stage) of Guedel Reflex stimulation may lead to coughing, retching, swallowing stertor or spasmodic arrest of breathing at any stage of ether anesthesia During maintenance these circumstances usually occur only in the lighter upper strata, but they may appear even in complete anesthesia Respiratory paralysis is a late toxic manifestation, and since it is well beyond any therapeutic requirement of

22	40	F	Sequestrectomy	Nitrous oxide-ether	7	10	16	10	20 M
23	43	M	Cholecystectomy	Nitrous oxide-ethylene-ether	6	4	15	14	18
24	53	M	Laparotomy	Ethylene-ether	6	14	20	18	24 S
25	26	F	Laparotomy	Spinal-ether	8				21
26	15	M.	Craniotomy	Ethylchloride and rectal	6	5	6		10
27	16	F	Appendectomy	Ethylene	5	9	14	12	12
28	26	M.	Skin graft	Ethylene	8	10	17	16	20 C
29	13	M	Skin graft	Ethylene	7	12	14	10	14
30	19	F	Gastroenterostomy	Ethylene	5	10	18	12	15
31	40	F	Perineorrhaphy and trachelorrhaphy	Ethylene	8	12	14	13	17
32	26	F	Dilatation and curettage cauterization	Nitrous oxide	7	10	17	14	16
33	17	F	Dilatation and curettage	Nitrous oxide	5		10		8
34	14	M	Exploratory puncture—lung abscess	Nitrous oxide	6		12		12
35	20	M	Tonsillectomy	Nitrous oxide	12	16	16	10	18 S
36	34	M	Appendectomy cholecystectomy	Nitrous oxide	10	14	22	16	22 S
37	52	F	Colpotomy	Nitrous oxide	6	10	12	11	16 M
38	19	M	Biopsy—knee	Nitrous oxide	6	4	18	13	15
39	15	M	Adenectomy—cervical nodes	Nitrous oxide	10	18	34	21	27
40	13	M.	Skin graft	Nitrous oxide	6	9	13	11	11
41	29	M	Fracture—leg setting	Nitrous oxide	8	10	18		14
42	25	M.	Incision—thumb	Nitrous oxide	7	6	18	18	20

M—surgical manipulation E—emesis S—struggling LA—lighter anaesthesia; RO—respiratory obstruction C—cyanosis.

anesthesia, opportunity has not been afforded for its study in the present relation Indeed, modern methods have limited the present observations of the venous pressure changes in the maintenance period to the upper strata of the third stage in the main

With the thought of determining the possible effects of such alterations in normal respiratory rate, depth and rhythm upon the venous pressure, 42 subjects were studied through varying periods of general anesthesia The Hooker-Eyster apparatus (17) for indirect venous blood pressure determination was utilized In addition to its established accuracy this method has the great advantage of affording the opportunity for rapidly repeated observations without serious technical difficulty All anesthetics were administered by Dr R M Waters or his assistants, thus insuring a measure of uniformity—subject, of course, to the exigencies of the individual case Early in the study the impracticability of coordinating the results on the basis of duration of the anesthesia led ultimately to the exclusion of this detail For notes as to the stage of anesthesia Dr Waters and his assistants are responsible In table 1 the results have been collected The lowest and the highest venous pressure determinations have been recorded for the periods of induction and of maintenance in each case

The ranges of ages and of operative procedures are wide The number of anesthetic agents utilized is small and criticism may well be directed toward this detail However, although nitrous oxide or nitrous oxide-ethylene constitute an overwhelming majority of the group (29 of 42), representative series with ether after induction by nitrous oxide or ethylene (6) and with ethylene as the sole agent (5) have been studied Prior to the anesthesia a single case in the entire group (case 35) exceeded the upper limit of normal venous pressure, 11 cm of water (18) In the induction phase physical effort and interference with the normal rhythm of respiration were routinely observed to induce prompt rises in the venous pressure The low readings of the induction phase were in excess of the pre-anesthetic levels in all except 5 instances where readings were available (36 cases) At this period the normal level was exceeded in 10 instances of the lowest recorded venous pressure of the 36 cases, whereas the high individual levels for the induction period exceeded the normal levels in 36 of 40 cases with adequate data Of the 4 remaining cases

no rule can be formulated to explain their exception Significantly in the maintenance stage without recorded exception (36 cases) the figures for the low levels exceeded the pre anesthetic pressures, whereas

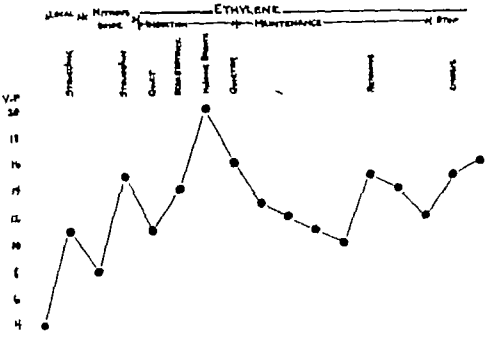

FIG 1 A TYPICAL CURVE SHOWING VARIOUS FACTORS AFFECTING VENOUS PRESSURE DURING ANESTHESIA

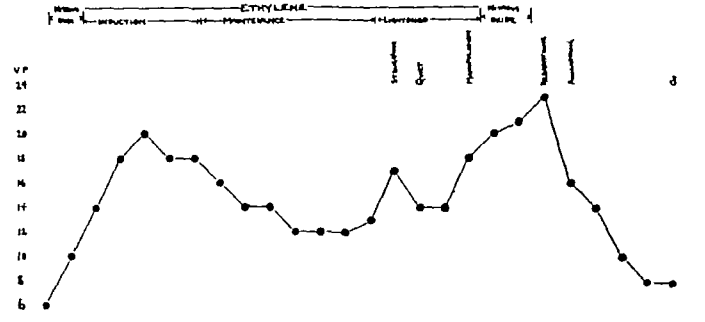

FIG 2 A TYPICAL CURVE SHOWING VARIOUS FACTORS AFFECTING VENOUS PRESSURE DURING ANESTHESIA

in 9 instances the low levels for the maintenance period were below those for the stage of induction As to the high levels of the maintenance period 20 of 40 comparative figures showed levels lower than

or equal to those of the induction Explanatory legends in table 1 account for unusual rises during maintenance A better conception of these circumstances may be gathered from characteristic curves (figs 1 and 2)

In both curves the prompt rise during the induction of anesthesia is striking In figure 1 the circumstances of physical exertion and respiratory interference reflect themselves immediately in venous pressure elevations Attention is also directed to the fact that, although the level of the venous pressure tends to fall after induction, still throughout the most regular period of maintenance a plateau of venous pressure is established above the pre-anesthetic level This phenomenon is better represented in figure 2 Release from anesthesia is marked in both curves by elevation of the venous pressure dependent upon varying conditions In figure 2, the venous pressure has been followed for a longer period after the withdrawal of the anesthetic agent, hence it constitutes a more characteristic curve for this period

Two collateral observations have been made In the first place, on several occasions carbon dioxide has been exhibited in varying proportions with an invariable rise of the venous pressure in spite of the over-ventilation of the subject Secondly, on two occasions isolated studies of the venous pressure have been made under the circumstance of surgical shock In each instance a low level was recorded Unfortunately, the previous trend of the venous pressure curve was not known and these observations are too detached to have other than a suggestive importance

CONCLUSIONS

The significant changes in the venous pressure under the conditions of general anesthesia may be summarized as follows

1 Coincident with the increased muscular effort and the altered respiratory function of the induction of anesthesia pronounced increases in venous pressure are noted

2 Thereafter succeeds a plateau of somewhat elevated venous pressure throughout the maintenance of anesthesia

3 Alterations in this plateau apparently depend upon reflex stimuli usually in a period of lightened anesthesia

4 Release from the anesthesia is marked by elevations in the venous pressure dependent on such acts as retching, vomiting, etc

5 Carbon dioxide operates to increase venous pressure

No effort is made to link these changes in the venous pressure under general anesthesia in a causal relation with the circulatory accidents of operation The demands of ordinary life are in excess of those attending an operation under a carefully administered general anesthetic, as Marvin has stated Nevertheless, as a measure of this particular load on the right heart, the above data are interesting

Grateful acknowledgement is made for the hearty coöperation of Dr R M Waters and his staff in this study

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VARIATIONS IN THE CARDIAC OUTPUT OF MAN

V The Cardiac Output of Man During the Malaise and Pyrexia Following the Injection of Typhoid Vaccine

By ARTHUR GROLLMAN

(From the Physiological Laboratory, School of Medicine The Johns Hopkins University, Baltimore)

(Received for publication May 23, 1929)

While investigating the effect of the environmental temperature on the cardiac output of man, it was observed that the values obtained on a subject who, several hours previous to the experiment, had received an injection of typhoid vaccine, were much higher than the values which had previously been obtained in repeated determinations on the same individual This unexpected increase in cardiac output was attributed to the effect of the reaction to the foreign protein injected and it was thought worth while to extend the observation on a number of other individuals The problem seemed of interest because it enabled one to determine the reaction of the heart to slight degrees of malaise and fever Since the nature of this reaction to foreign protein, as observed after the injection of typhoid vaccine, is in many respects similar to the reaction following certain infectious processes, the results should also throw light on the cardiac changes which might be expected to accompany these conditions Exact data of the clinical variations of the cardiac output are extremely rare because of the great inaccuracies and difficulties which attend such determinations, and hence any additional data bearing on this problem are highly desirable

METHODS

The present determinations of the cardiac output were carried out by the use of acetylene (1) in the method previously described (2) By the use of this gas an extremely high degree of accuracy is easily obtainable and the results quoted should not be in error beyond ± 5 per cent

All of the subjects used in the present investigation were young, healthy medical students, who were sufficiently well acquainted with the general procedure to avoid the vitiating effects of any excitement or other psychic disturbance In all, except two, of the cases studied data were available for the values of the various functions studied before the injection The control determinations on any one individual were always made at the same time of the day as were the determinations after the injections in order to avoid any diurnal variations of the cardiac output After at least one-half hour's rest in a steamer chair, the various determinations were performed, with the precautions described in previous studies (3, 4)

The subjects for the present study were selected from those who had shown a rather severe reaction to a previous injection of the typhoid vaccine Except in the case of subjects 6 and 7, the results refer to the effects of the second of a total of three weekly injections, in which one billion typhoid bacilli were injected in the usual manner into the triceps muscle of the arm The results on subject 6 were obtained after the first of the three injections (500 million bacilli) and those on subject 7 were obtained after the third injection

In calculating the cardiac output during fever, it is necessary to take into account the diminution in solubility of the foreign gas used, as a result of the increased temperature of the blood As previously noted (1) the temperature of this blood is not exactly known but has been estimated for the normal condition as 37 5°C The temperature coefficient for the solubility of acetylene in blood is about 12 cc per liter per degree centigrade (5) Hence, by subtracting this value from 740, the solubility of acetylene in blood at 37 5° (6), for every degree centigrade rise in body temperature, one obtains a value which is to be substituted in the equation used in calculating the heart output during pyrexia (1)

RESULTS

The results of this study are given in table 1

The most complete series of results are those quoted on Subject 1 In this case determinations were made at intervals during the first 24 hours after the injection This subject had a particularly violent reaction to the vaccine Two hours after the injection (table 1 and

TABLE 1

The effect of the injection of typhoid vaccine on the cardiac output pulse rate, blood pressure, temperature (oral), and oxygen consumption

Subject number	Condition	Pulse rate	Blood pressure	Temperature (oral)	Oxygen consumption	Arteriovenous oxygen difference	Cardiac output
				F	*cc. per minute*	*cc. per liter*	*liters per minute*
1	24 hours before injection	74	105/75	97 6	240	63	3 81
	2 hours after injection sore arm, vague soreness of joints, not perceptibly ill	86	109/80	98 7	281	60	4 68
	7 hours after injection, general malaise	102	118/83	100 7	322	50	6 44
	12 hours after injection, extremely ill, practically prostrate	120	124/70	103 8	363	75	4 84
	19 hours after injection feeling weak and generally ill but much improved over time of preceding determination	100	108/65	101 1	330	65	5 09
	5 days after injection	70	103/72	97 5	238	63	3 78
2	24 hours before injection	78	108/70	97 3	284	63	4 51
	3 hours after injection no subjective reactions	80	112/71	97 7	280	55	5 09
	21 hours after injection head ache and slight malaise	88	103/70	98 5	300	60	5 00
	1 week after injection	76	100/60	97 7	288	65	4 43
3	Before injection	74	116/74	97 8	295	60	4 92
	23 hours after injection malaise and headache	90	158/84	99 8	318	60	5 30
	1 week after injection	80	142/82	97 8	308	62	4 97
4	18 hours after injection slight feeling of malaise	90	106/69	98 8	239	52	4 60
	1 week after injection	68	101/64	97 1	230	56	4 11
5	21 hours after injection head ache and general malaise	84	98/68	99 1	282	60	4 70
	6 days after injection	62	110/73	97 1	264	65	4 06
6	Before injection	70	103/65	97 5	245	62	3 95
	18 hours after injection, very slight malaise	80	117/70	98 0	274	66	4 15
	1 week after injection	62	105/65	97 6	236	60	3 93

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TABLE 1—*Concluded*

Subject number	Condition	Pulse rate	Blood pressure	Temperature (oral)	Oxygen consumption	Arteriovenous oxygen difference	Cardiac output
				°F	*cc per minute*	*cc per liter*	*liters per minute*
7	Before injection	60	105/70	98 0	220	63	3 49
	20 hours after injection, very slight malaise	82	108/65	98 3	225	62	3 63
	1 week after injection	62	104/68	98 0	220	58	3 80
8	Before injection	70	105/70	97 6	240	60	4 00
	3 hours after injection, slight malaise	80	117/82		280	58	4 83
	1 week after injection	70	105/70	97 5	238	60	3 97

fig 1) marked changes from the resting values of the normal were already obtained At this time there was a vague sense of soreness in the joints but no severe subjective symptoms Nevertheless, there was a mild pyrexia, an increase of 20 per cent in the oxygen consumption, and a corresponding increase in the cardiac output The heart may be considered at this time as merely responding to the increased metabolism, with but slight diminution in the oxygen utilization of the blood

At the time of the second determination, the subject was feeling quite ill and all the functions studied were greatly elevated The third determination on this subject was made at the height of his illness, 12 hours after the injection The subject was practically prostrate Although the pulse, blood pressure, body temperature, and oxygen consumption were now at their maxima, the cardiac output was greatly diminished over its previous value, when the subject was less ill This change was brought about by a great increase in the oxygen utilization of the blood This also occurred in the case of the other subjects studied Thus in the case of the second experiment on subject 2, the cardiac output is slightly greater than that of the third experiment although the malaise, pulse, fever, and oxygen consumption were greater in the latter experiment It thus appears that the change in malaise and pyrexia and the increase in cardiac

output do not occur together Instead, the greatest increase in cardiac output occurred soon after the injection when the pyrexia and malaise were at a minimum About 15 to 24 hours after the injection when the subjective feelings were severe, the cardiac output showed lesser changes than it had previously We must thus conclude that

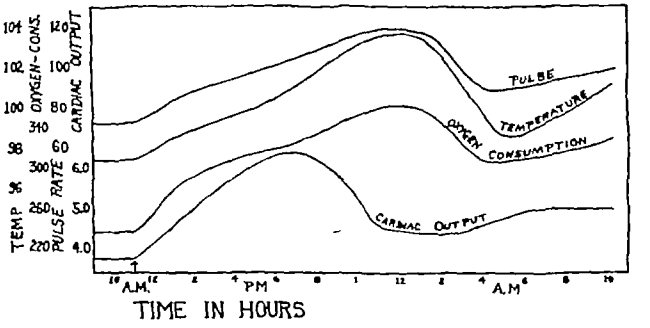

FIG 1 GRAPHIC REPRESENTATION OF THE CHANGES IN PULSE RATE, TEMPERATURE (ORAL), OXYGEN CONSUMPTION AND CARDIAC OUTPUT DURING THE 24 HOURS FOLLOWING THE INJECTION OF 1 CC. OF TYPHOID VACCINE

The axis of abscissae represents the time of the day in hours At the point indicated by the arrow (11 00 a.m), the injection was made The horizontal portions of the curves represent the normal values of the various functions studied as found previous to the injection The cardiac output is expressed in terms of liters per minute the oxygen consumption in cc. per minute, and the temperature in degrees Fahrenheit The subject's malaise followed the temperature, pulse rate, and oxygen-consumption curves, being at its maximum at midnight, 13 hours after the injection The malaise then subsided but increased again during the following morning and continued throughout the following day and night with a fever of over 100°

the injection of foreign protein causes at first an increase of the cardiac output which then partly subsides during the later stages of the reaction when the subjective feelings are at their maximum

These results as obtained on subject 1 during the first 24 hours following the injection, are graphically represented in figure 1

In order to compare the values of the cardiac output and other

functions studied during the subject's reaction to the typhoid vaccine with the normal values of these functions, it was necessary to obtain data on days before the injection or after recovery It may be objected that such comparisons are not permissible since the heart output is usually considered as varying widely from day to day This objection, however, is invalid, for the concept of a variable cardiac output under normal conditions is based upon erroneous data Unpublished results[1] by the author have shown that if proper precautions be taken to avoid such factors as psychic disturbances, temperature variations, food, etc , constant results may be obtained from day to day Hence the results obtained during the malaise following the injection of the vaccine may be compared to those obtained when the subject was normal, despite the fact that the two sets of data were obtained on different days This is further demonstrated by the close agreement between the results obtained on the day before the injection and those obtained some days later (table 1) Except in the case of subjects 1 and 2, the data were obtained in the morningon the subject's arrival at the laboratory in the basal condition When basal determinations were impossible as in the case of the determinations on subjects 1 and 2, the control experiments were made at the same hour of the day and under the same conditions as the experiments after the injection Such determinations were always made some hours after the ingestion of a very light meal, under which conditions as has been demonstrated (10), the value of the cardiac output is essentially that of the basal condition

DISCUSSION

Inspection of table 1 and figure 1 shows the marked increases in the pulse rate which follow the injection of typhoid vaccine This increase in pulse rate was found to follow the subjective feelings of malaise and the pyrexia Since the cardiac output, as stated above, did not follow the malaise and pyrexia except during the early period

[1] Further evidence for this is furnished by the demonstration (11) of the possibility of predicting the cardiac output of normal individuals in the truly basal condition As has been previously demonstrated (11) one can judge, from a single determination of the cardiac output, the degree of its abnormality

of the reaction, it is evident that there is a marked variation in the output per beat of the heart During the early period of the reaction, there was, in general, a marked increase in the output per beat but at the height of the malaise, this increase was diminished

In general the blood pressure, after the injection of typhoid vaccine, shows only a moderate degree of variation from the normal There was, except in subject 5, a rise in the systolic pressure and usually a slight rise in the diastolic pressure, although the latter was at times diminished

The degree of pyrexia followed closely the subjective symptoms The increase in oxygen consumption, in turn, was proportional to the degree of pyrexia, as noted by Du Bois and his collaborators (7, 8)

The observed changes in cardiac output can be explained as resulting either from a direct stimulation of the heart or as a secondary effect of the increased metabolism The relatively slight changes in the arterio venous oxygen differences would support the view that the second of these factors is responsible for the cardiac changes Hence, the increased cardiac outputs following the injection of typhoid vaccine are to be considered as an attempt on the part of the organism to maintain a constant internal environment, in so far as the oxygen utilization of the tissues is concerned At the height of the malaise, the relative decrease in the cardiac output may be related, in part at least, to the decrease in the volume of blood flowing through the periphery (9) This decrease in the size of the peripheral vascular bed, would result in a great increase in the blood pressure were the latter not avoided by a diminution in the cardiac output

Bjerlöw and Liljestrand (12) found, in four cases of experimentally induced recurrent fever, an increase in the cardiac output proportional to the increased oxygen consumption encountered during the fever This is in accord with the present findings during the early stages of fever These authors failed to note, however, the failure of the cardiac output to follow the changes in oxygen consumption during the later stages of fever, as shown in the present work Due to the protracted nature of the fevers encountered clinically, this latter state of affairs is probably of greater practical significance than the changes occurring during the very early stages of fever

SUMMARY

A study was made of the cardiac output, pulse rate, blood pressure, temperature, and oxygen consumption of 8 individuals after the intramuscular injection of typhoid vaccine The cardiac output was found to be greatly elevated soon after the injection but did not follow the malaise and pyrexia throughout the course of the reaction At the height of the malaise the cardiac output, although still elevated above the normal, was nevertheless less than it was during the preceding period The pulse rate and oxygen consumption varied uniformly with the degree of malaise and the pyrexia The physiological implications of these results are discussed

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AN APPARATUS FOR THE PROLONGED ADMINISTRATION OF ARTIFICIAL RESPIRATION

II A Design for Small Children and Infants with an Appliance for the Administration of Oxygen and Carbon Dioxide

By LOUIS A SHAW and PHILIP DRINKER

(From the Departments of Physiology and of Ventilation and Illumination, Harvard School of Public Health Boston)

(Received for publication May 10 1929)

The apparatus herein described is similar in principle to that designed by Philip Drinker and Shaw (1), but with modifications which will more adequately meet the special requirements of infants and children up to twenty pounds in weight Though this apparatus has not as yet been available for clinical purposes, the authors believe that its efficacy has been assured both by the tests made with the apparatus already described (1), (2) and by the laboratory tests upon curarized cats in the respirator described in this paper

A few words will suffice to restate the principle upon which this apparatus operates The child is placed in a metal box or respirator which has a hole at one end through which the head protrudes and is sealed off by a rubber dam about the neck After the respirator has been closed, the body is then in an air-tight container with the head exposed to room air By means of an electrically driven air pump and valve arrangement connected to the respirator, alternate negative and positive pressures may be induced A negative pressure causes the chest to expand and air will flow into the lungs, while a positive pressure will compress the chest and cause the air to be expelled Thus a movement of the chest is induced which simulates the natural respiratory movements

CONSTRUCTION OF RESPIRATOR

The respirator is constructed of metal sheets about 3 mm thick, soldered or welded together The whole top is hinged from the side to form the lid and consists of a metal frame in which a heavy plate-

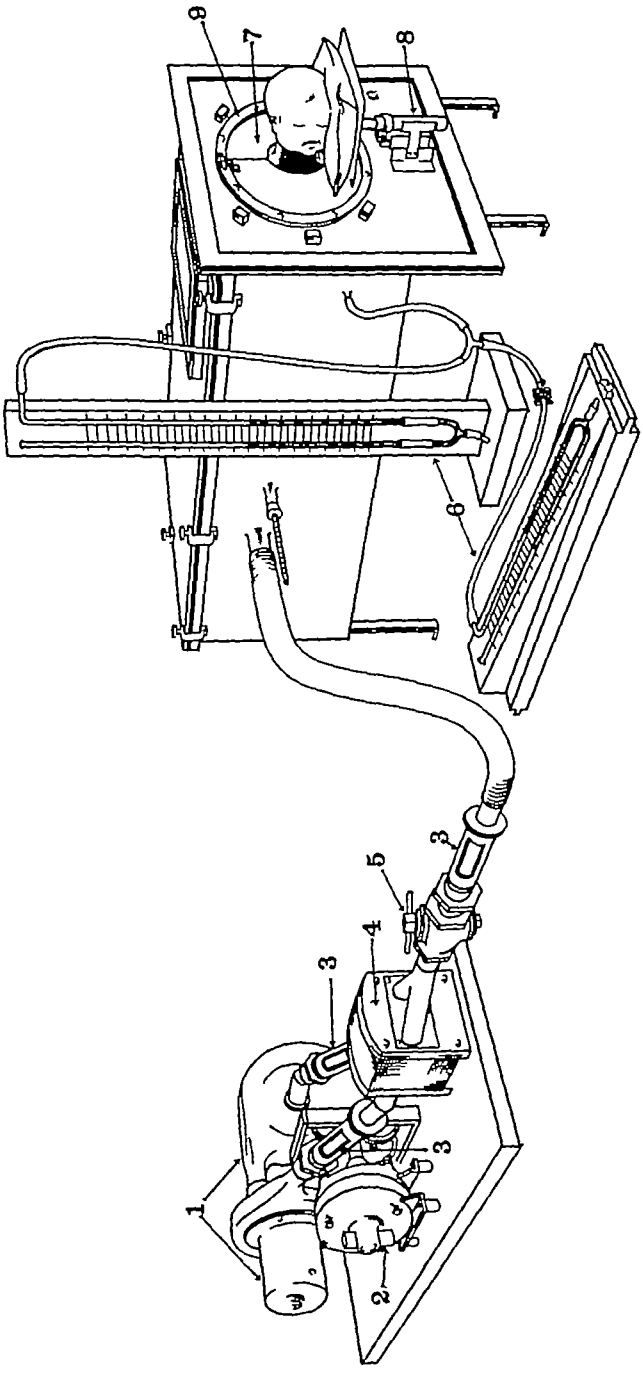

FIG 1 THE RESPIRATOR AND PUMP

1, pumps, *2*, motor, *3*, vents, *4*, alternate, *5*, valve, *6*, manometers, *7*, external shutters, *8*, adjustment for head rest, *9*, adjustable ring to hold collar in place

glass window is set in order that the body of the patient may be kept under observation The lid closes against a rubber gasket and is held fast by means of clamps which, when tightened, render the respirator proof against leaks

The head passes through a sheet of rubber with a hole in the center This is made in a mould in such a manner that the edge is reflected to form a collar which fits snugly to the neck (fig 1) This collar is made in various sizes, the rubber being thin enough to offer no discomfort As the periphery of the collar is reached the thickness of

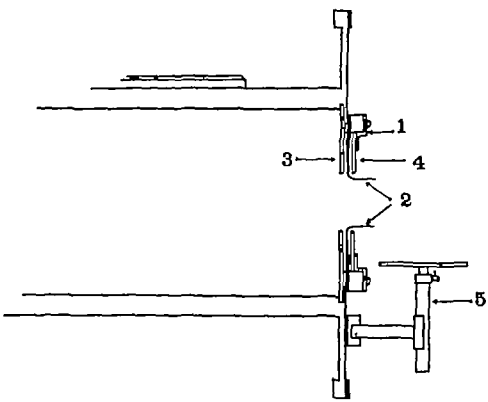

FIG 2 SAGITTAL SECTION OF RESPIRATOR

1, adjustable ring to hold collar in place, *2*, rubber collar, *3*, internal shutters *4*, external shutters, *5*, adjustment for head rest

the rubber is increased slightly, thus giving it sufficient body to act as a gasket when pressed against the ring (fig 2) about the head aperture

Having selected the appropriate collar, the neck opening must then be stretched sufficiently to permit the head to pass through comfortably This is effected by hand or by means of six hook-shaped metal bands which act as retractors When retractors are used the hooked ends are inserted in the opening of the collar and then drawn back and fastened in place, thus leaving an opening sufficient for the

passage of the head through the collar The hooks are then removed and the collar allowed to close in about the neck The entire procedure of adjusting the patient in the respirator for the administration of artificial respiration consumes less than one minute

In order to prevent the thin rubber collar from bulging under the air pressures in the respirator and thus causing both discomfort and leaks, it is necessary to give it support This is accomplished by two pairs of shutters which are cut out in such a manner that they fit the neck, and when closed, one pair on either side of the collar, the latter is so closely confined that movement is impossible

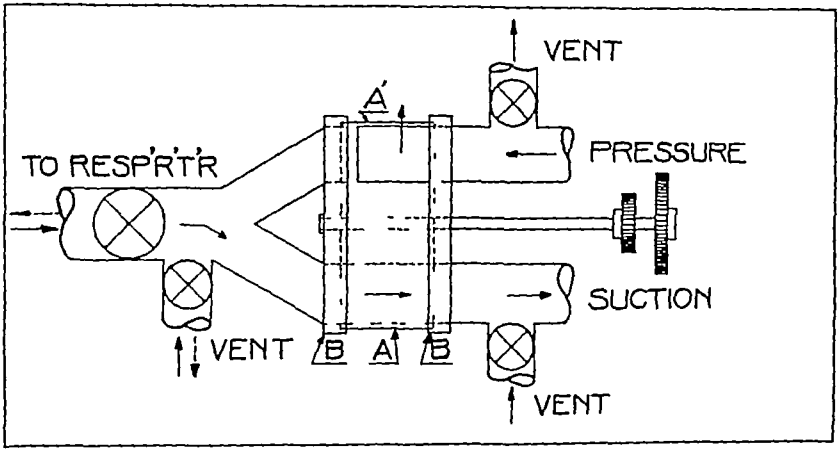

FIG 3 THE PUMP AND ALTERNATOR

The head-rest may be adjusted for any height It may also be swung upon a basal pivot into a horizontal position so that it does not constitute an interference while the dam is being adjusted about the neck

The pressures are created by one or two vacuum cleaners of the ordinary household type If this unit is too noisy, a small "Roots" blower may be substituted In either case, a single unit will do the work, although two units should be available in case one fails [1]

[1] We have found that the double or "twin" unit made by the Electric Blower Co , 352 Atlantic Ave , Boston, answers our requirements The "Roots" blower is made by the P H & F M Roots Co , Connersville, Ind

The approximate mechanical requirements are that the unit shall deliver about 25 cubic feet of air per minute (0 7 cubic meters) at approximately 15 inches (38 cm) of water pressure This specification is easily met by several makes of household vacuum cleaners, all of them relatively cheap and easily obtained

The air pump is connected to the alternator at the points marked *pressure* and *suction* in figure 3

A valve arrangement is necessary to give alternate positive and negative pressure within the respirator This valve, called the *alternator,* is shown in figure 3 as parts A, B, and B ′ The bearings are parts B and B′ and are stationary Part A is rotated by the shaft and gears (shown on the right) at any desired rate from 10 to 50 per minute

When the alternator is in the position shown in figure 3, air is drawn from the respirator and follows the direction of the arrow down the lower half of the Y-tube, through the alternator to the source of suction The discharge side of the pump blows air back through the upper half of the alternator (*pressure* connection) and follows the arrow up and out through part A′ When the alternator is rotated 180°, the reverse takes place, viz , air is drawn from the outside air through the bottom of the alternator at A, passes through the pumps, and is blown back through the upper half of the Y-tube and thence into the respirator

The outlets, indicated as *vents,* are helpful in controlling the pressures applied to the respirator By opening the *pressure* vent and closing the *suction* vent, the respirator is kept alternately under negative and then atmospheric pressure By opening the suction and closing the pressure vent, alternate positive and atmospheric pressures are obtained By closing both pressure and suction vents, alternate positive and negative pressures are obtained

The vent on the Y tube (left) side may be placed either as shown or on the respirator itself It permits by passing of some of the air to or from the respirator and thus controls the magnitude of the pressure variations The valve on the main pipe serves the same purpose We find it convenient to have both valve and vent

A water manometer connected to the respirator records the pressures while the pump is in action A second water manometer, also connected to the respirator, but inclined at such an angle that the ex-

cursion of the water column is increased ten-fold, is used when the pump is shut off, to detect the presence of respiratory movements Under these conditions the respirator acts as a plethysmograph in which the changes in volume due to the movement of the chest may be recorded in terms of pressure changes

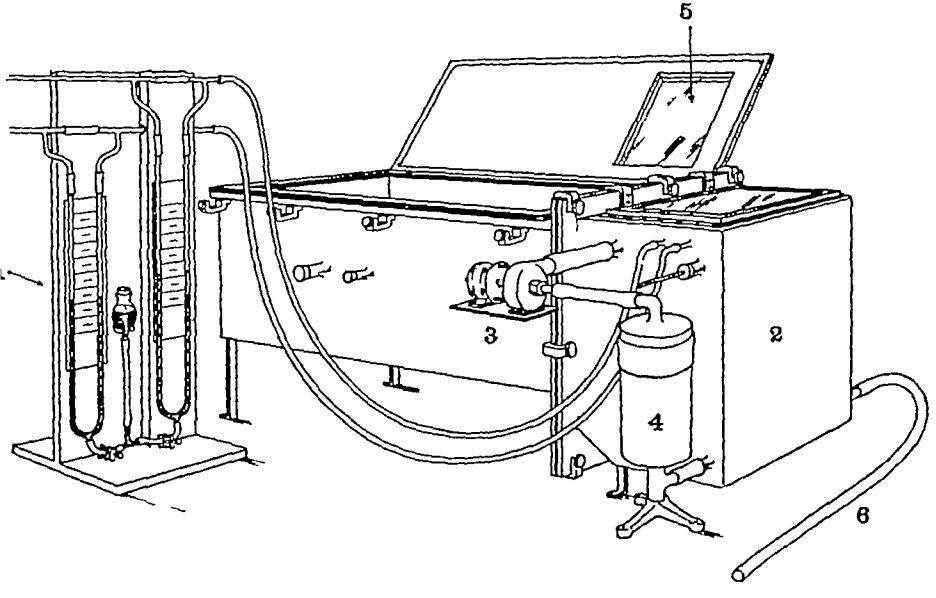

FIG 4 THE RESPIRATOR USED FOR THE ADMINISTRATION OF CARBON DIOXIDE AND OXYGEN THERAPY

1, flow meters, *2*, gas hood, *3*, impeller blower (Collins type), *4*, soda-lime can, *5*, window, *6*, tube for escape of gas flow

THE ADMINISTRATION OF CARBON DIOXIDE AND OXYGEN

When it is desired that the patient should breathe an atmosphere enriched with oxygen or carbon dioxide, the head may be inclosed in a chamber or hood (fig 4) and a mixture of air and oxygen allowed to flow through The hood has a glass top to permit observation of the head of the patient It is clamped against the end of the respirator with a rubber gasket intervening to render the compartment air-tight Air and oxygen may be admitted to the hood through flow meters which control the rate of flow There is a rubber tube of 2 cm bore and 75 cm long attached to the hood, the purpose of which is

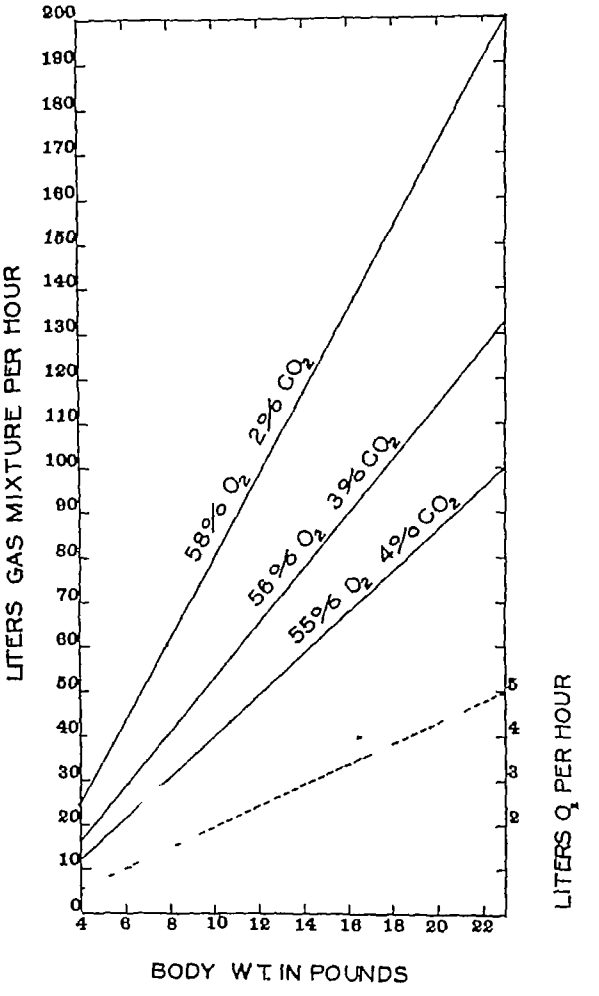

FIG 5 THE RATE OF GAS FLOW FOR CARBON DIOXIDE AND OXYGEN THERAPY

Ordinate at left, rate of flow of gas mixture composed of equal parts of air and oxygen, ordinate at right, rate of oxygen intake per hour

to permit the escape of the gas mixture flowing into the hood and which at the same time is of such a size as to prevent the influx of room air during inspiration from entering the hood and thus diluting the gas mixture The oxygen is supplied from a compression cylinder and the air from a similar source or from a compressed air line The concentration of oxygen in the hood is regulated by varying the relative rates at which oxygen and air are admitted

It has been shown that 60 per cent of oxygen in the respired air can be used without injury to the lungs, but that higher concentrations may be dangerous If, on the other hand, we attempt to safeguard the patient by reducing the oxygen concentration to about 40 per cent, much of the advantage of oxygen therapy will be lost When air and oxygen are mixed in equal parts the resultant mixture contains 60 5 per cent of oxygen If the gas mixture is allowed to flow at a sufficiently high rate, the oxygen consumed by the patient will have only a negligible effect upon the concentration of oxygen in the hood This point will be made clear by reference to figure 5, in which the rates of flow are given for children according to their weight Suppose, for example, that we desire to administer oxygen therapy to a child weighing ten pounds This is accomplished by running the 60 per cent oxygen mixture through the hood at a rate of 80 liters per hour To obtain this mixture it is only necessary to regulate the air flow at 40 liters per hour and the oxygen at the same rate as read off on the flow meters Eighty liters of a 60 5 per cent oxygen mixture contain 48 4 liters of oxygen Reference to the broken curve of figure 5 shows that a child weighing ten pounds will use up about 2 liters of oxygen per hour The resultant mixture in the hood will consequently be about $\left[\frac{48\,4 - 2\,0}{80}\right]$ 58 per cent of oxygen instead of 60 per cent Samples of gas withdrawn from the hood show that the oxygen does not depart from the calculated concentration by more than 1 per cent

If it is desired to remove the carbon dioxide completely, then a blower similar to that used with a Benedict metabolism apparatus may be attached to the hood and the air kept in circulation through soda lime On the other hand, if it is desired to administer carbon dioxide, then, by regulating the rate of gas flow through the hood, the carbon dioxide in the expired air may be built up to any desired

level When the gas flow through the hood is 50, 33 and 25 times as rapid as the rate of carbon dioxide excretion, then the concentration of carbon dioxide will be 2 ± 0 5 per cent, 3 ± 0 7 per cent, and 4 ± 1 per cent, respectively, the variations in per cent representing the individual variations in the metabolic rate of children of the same weight As an example we may take once more the child of ten pounds Such a child will excrete about (0 8 × 2) 1 6 liters of carbon dioxide per hour, which added to 80 liters will give a concentration of $\left[\frac{1\,6}{80}\right]$ 2 per cent carbon dioxide If it is desired to administer 4 per cent carbon dioxide to this child, then the gas flow must be reduced to 40 liters per hour At this rate the oxygen consumed will reduce the oxygen concentration of the respired air to 55 5 per cent This, however, is not a significant reduction

It must be understood that by a few simple calculations any concentration of oxygen which may be desired can be passed through the hood by altering the relative rates of flow of oxygen and of air

The hood may be used during the artificial respiration of the patient, or, with the lid left open, the respirator may be made quite as comfortable as a bed, while carbon dioxide or oxygen is administered to children who are breathing spontaneously

ARTIFICIAL RESPIRATION OF CURARIZED CATS

In order to test the efficacy of our apparatus in cases of suspended or impaired respiration, a series of experiments was carried out upon cats whose respiration had been paralyzed by an injection of curare An intraperitoneal injection of barbital sodium rendered the cats quiescent and insensible to the operation involved by the insertion of a tracheal cannula After the cat had been placed in the respirator, the tracheal cannula was connected to Tissot values and the minute volume of the normal breathing was determined by a collection of the expired air in a spirometer The respiration was then completely suspended by an injection of curare through the external jugular, and respiration sustained by the respirator

By means of the system of valves and vents attached to the air ducts of the pump and alternator, the pump can be made to create any degree or combination of pressures in the respirator which may

be desired positive alternating with negative, positive alone or negative alone, and any degree of pressure up to 50 cm or more of water The effect of these variations in kind and degree of pressure

TABLE 1

*Per cent deviation from the normal respiratory volume resulting from alternate positive and negative pressure, negative pressure alone, and positive pressure alone**

	Experiment	Deviation from normal respiratory volume at varying pressures (cm H_2O)						
		4	6	10	12	15	20	30
		per cent	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
Positive and negative	1	−17	+27	+155				
	2				+44	+62	+280	+650
	3	−31	+84	+190		+303	+451	+766
	4		+1	+57		+193	+268	+563
	5		+27	+87		+192	+366	
	Average†	−24	+34	+122		+229	+362	+665
Negative only	1			+77		+165	+300	
	2				+65	+67	+339	+672
	3		−18	+170		+269	+427	+741
	4		−52	+1		+127	+211	+545
	5							
	Average†		−35	+83		+187	+313	+643
Positive only	1					−12	+10	+31
	2							
	3			−12		−6	−7	−7
	4			−40			−27	−12
	5			+3			+10	+18
	Average†			−16		−9	−3	+8

* The + sign signifies that the ventilation is in excess of normal, and the − sign, less than normal

† Experiment 2 not included in average

was measured by the volume of expired air collected in the spirometer per minute The alternator was set to give 25 breaths per minute The results of five experiments are given in table 1, which gives the per cent deviation from the normal respiratory volume The same

data are shown in graphic form in figure 6 The points give the average value for all experiments except no 2, the omission of which will

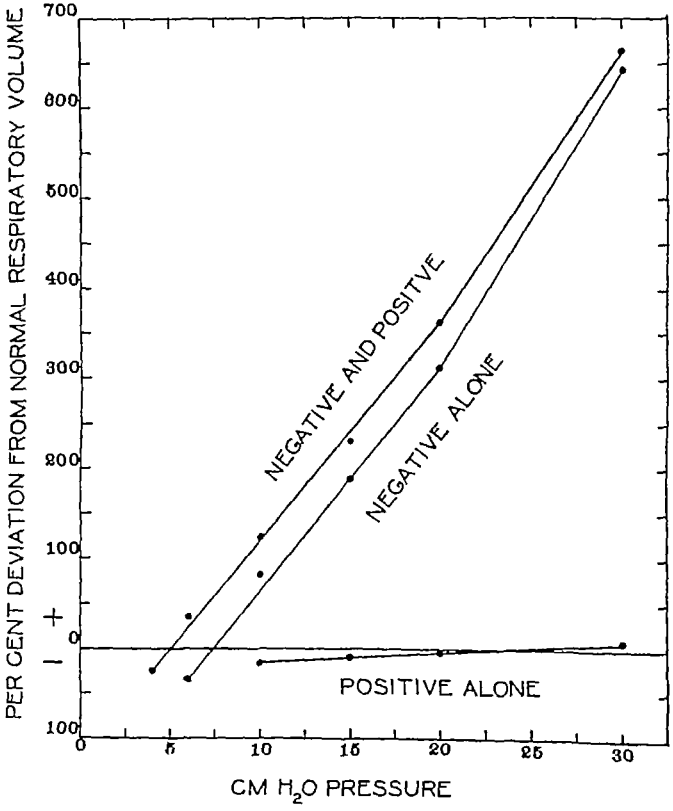

FIG 6 RESPIRATORY RESPONSE OF CURARIZED CATS TO DIFFERENT PRESSURES

be explained The points which fall below the 0 abscissa indicate the degree to which the ventilation was inadequate, those above the 0

abscissa indicating ventilation in excess of normal It will be observed, from inspection of table 1, that there is a large individual variation in the respiratory response to a given pressure At an alternating positive and negative pressure of only 6 cm of water, the ventilation proved to be adequate in all cases except cat no 2, in which case it was necessary to increase the pressure to 12 cm in order to equal the normal respiratory volume

As might be expected, the alternate application of negative and positive pressure was somewhat more effective than the negative pressure alone The fact that an even greater difference does not occur is probably due to the fact that, when well stretched into the inspiratory position the chest tends to snap back to an expiratory position rather than to the normal resting position, thus expelling a certain amount of supplementary air The curves under discussion indicate that even when an increase of 650 per cent of the tidal volume has been reached, there is no tendency for the thoracic wall to offer increased resistance to the stretching effect of the negative pressure, on the contrary, instead of becoming flattened the curves become slightly steeper Since no pressures above 30 cm of water were used we cannot say at what point the curves would commence to flatten out

The positive pressure used alone was just sufficient to sustain the normal ventilation in four out of the five experiments, and showed but little tendency to increase with increasing pressure This is about what we should expect in consideration of the fact that it is quite impossible to over-ventilate a human subject by the Schafer method, which operates by positive pressure alone Cat No 2 proved to be so resistant to positive pressure alone that it was impossible to sustain life without the assistance of about 12 cm of negative pressure, and was equally resistant to negative pressure until 20 cm had been reached, at which pressure it approximated the average response of the other four cats Except in the instance cited the ventilation was normal at an alternating positive and negative pressure of about 6 cm of water These results agree very closely with those of Philip Drinker and Shaw (1) using intact human subjects They found that a pressure of 6 to 10 cm of water was sufficient to cause normal respiration, while increased pressures caused a propor-

tionate increase in the respiratory volume which was quite beyond the power of the subject to resist

At intervals throughout these experiments the pump was shut off and the onset of cyanosis was followed by observing the color of the tongue, which was drawn from the mouth and held in a convenient position After asphyxia had progressed as far as we deemed consistent with life, respiration was resumed and the normal color of the tongue returned in about twenty seconds

An experiment was done to determine the effect of rate of respiration upon the volume of air taken into the lungs at a given pressure It will be observed from inspection of table 2 that the tidal volume when

TABLE 2

Effect of respiratory rate upon the tidal volume, using alternate positive and negative pressures 22 and 37 times per minute

Pressure	Tidal volume	
	Rate 22	Rate 37
cm H_2O	*cc*	*cc*
±6	23 1	23 8
±10	34 1	34 2
±15	54 1	52 8
±20	85 0	87 7

the rate of breathing is 22 per minute is practically identical to that obtained at a rate of 37 It becomes clear from these figures that the filling of the lungs is complete for any given pressure at all rates of breathing within the physiological limits

SUMMARY

1 An apparatus has been described which will induce breathing in children suffering from respiratory failure While the body is inclosed in an air-tight chamber, the head protruding through a rubber dam at one end, the chest and abdomen will rise and fall in response to alternating negative and positive pressures created within the chamber by means of an air pump

2 By means of an air tight chamber which fits over the head the carbon dioxide and oxygen content of the respired air may be regulated to meet the demands of carbon dioxide or oxygen therapy

3 The operation and efficacy of the respirator has been tested upon curarized cats

We wish to express our thanks to Mr Frederick J Christensen, Superintendent of the Machine Shop of the Harvard Medical School, for his co-operation and valuable suggestions in perfecting the technical details of our apparatus

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THE MEASUREMENT OF CAPILLARY PRESSURE UNDER NATURAL CONDITIONS AND AFTER ARTERIOLAR DILATATION, IN NORMAL SUBJECTS AND IN PATIENTS WITH ARTERIAL HYPERTENSION AND WITH ARTERIOSCLEROSIS[1]

By LAURENCE B ELLIS and SOMA WEISS

(From the Thorndike Memorial Laboratory, Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston)

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INTRODUCTION

Measurements of capillary pressure have been made by various observers The significance of the results is under dispute and there is no unanimity of opinion either as to the best method for determining capillary pressure or as to the absolute value of that pressure in man The importance of the subject is self-evident Not only is it highly desirable to know the pressure of the blood in those vessels which act as distributing stations for the tissues, but the normal capillary pressure must first be known before abnormal pressures can be evaluated The knowledge of the capillary pressure is particularly important in arterial hypertension and in arteriosclerosis as an aid to our understanding of the nature of these conditions The investigations reported in this paper concern the pressure in the capillaries of people with normal cardiovascular systems, and of patients with arterial hypertension and arteriosclerosis, both under natural conditions and when the arterioles have been artificially dilated

Since von Kries (1) (2) first described a method for the determination of capillary pressure in 1875, many observers have reported values which have ranged from 4 to 70 mm of Hg No attempt will be made here to review completely the literature This has been adequately done in the reviews of Friedenthal (3), Danzer and Hooker (4), and Tigerstedt (5)

[1] This investigation was aided by a grant from the William W Wellington Research Fund of the Harvard Medical School, and by a grant in memory of Francis W Peabody by the Ella Sachs Plotz Foundation

METHODS

There are three general methods for the measurement of capillary pressure (A) The oldest and that most frequently employed is that of estimating the pressure necessary to cause a certain degree of blanching of the skin The values, expressed in millimeters of mercury, obtained with this method for the normal capillary pressure by some of the investigators, are as follows von Kries (2), 37 7, Natanson (6), 70 5, von Basch (7), 25–30, Rotermund (8), 26 8, von Recklinghausen (9), 52 5, Schiller (10), 40, Basler (11), 7, Landerer (12), 17–25, Goldmann (13), 8 5, Krauss (14), 6–9, Briscoe (15), 23 5, Krogh (16), 8 There is obviously a great discrepancy in the results This is partly due to the various types of apparatus employed and partly to the various criteria of paling

(B) The second method is based on the observation under the microscope of individual capillaries and the determination of the pressure necessary to cause an alteration in the velocity of blood flow through such a vessel This technic was first devised by Roy and Brown (17) (18), in 1879, who observed that the capillaries in the web of a frog's

ings of 3 5 to 6 0 mm of mercury Landis (37) has employed a some what similar technic in studying capillary pressure in the frog's mesentery and finds the pressure to average 11 mm of Hg

It will be seen that there are objections to each method

(A) The first and paramount objection raised against the skin blanching method is that the skin color is largely determined by the blood in subpapillary venous plexuses, and therefore the pressure deter mined is not that of the capillaries but rather of the minute venules It is true that the skin color is chiefly due to blood in the subpapillary venous plexuses and that in blanching the skin these plexuses are compressed Nevertheless, when external pressure is applied over an area of several square centimeters, as is done in the skin blanching method, it seems reasonable that this pressure must be of the same order of magnitude as that normally prevailing in the capillaries, and not the venules, in order to cause the venules to collapse and the skin to pale If a pressure is applied which is only equal to the normal pressure of the venules, there may be a tendency for a compression of these vessels, but immediately the higher pressures in the capillaries which are directly adjacent to the venules will be transmitted to them and the venules will reopen and remain open until the external pressure is raised to a point equal to the normal capillary pressure Therefore, although the blanching of the skin is indeed due to a closure of the minute venules, the pressure relationships obtained may well be as accurate an index of true capillary pressure as is obtained by the more complicated and not undisputed method of microscopic examination

The blanching method is also criticized on the grounds that different skins vary greatly in their intensity of coloring, due to the degree of dilatation of the subpapillary plexuses, and that the ease of determina tion of blanching is dependent not only on the degree of color but on the visual acuity and skill of the observer

(B) In the method of microscopic examination one is studying very few capillaries in one location, i e., the nail bed Even among these few, pressure values vary either because of varying tone of individual capillaries or because different capillaries lie at different depths from the surface, and certain of them receive greater protection than others from the surrounding tissues It is also recognized that considerable spontaneous variations occur in the blood flow through the individual

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(C) The third method is that of direct measurement of the pressure of the blood by puncturing the capillary Krauss (14), Basler (11), (25), and E Weiss (26) independently attempted this by pricking through the skin and determining the pressure of the blood as it emerged Basler found a pressure of 7 mm of mercury, and Krauss (14) obtained pressure values of from 7 to 10 mm of mercury Carrier and Rehberg (27) in a beautiful, but difficult experiment have cannulated a single capillary with a fine pipette and obtained pressure read-

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capillary loop and the differentiation whether the change in the blood flow is due to the induced pressure or to spontaneous change may be difficult Thus a less satisfactory composite picture of capillary reaction is obtained than when one studies the mass reaction at one time of all of the capillaries within a given area

Another objection may be raised, namely, that the capillaries of the nail-bed are particularly subject to external influences, such as trauma and light, and they may not represent the pressures in other capillaries The technic requires considerable exposure to light, heat and trauma, and thus arteriolar dilatation may occur which distinctly raises the capillary pressure Moreover, the criteria for determining capillary pressure are by no means established, and it is certain that the higher values obtained by this method are really measurements of arteriolar pressure transmitted to the capillaries when the capillary blood flow stops because of the compression of these vessels

(C) The third method, that requiring perforation of the skin and direct measurement of the pressure, is open to serious objections If a simple puncture is made it is obvious that it is quite impossible to know definitely what class of vessels has been perforated When the capillary is actually cannulated, as by the technic of Carrier and Rehberg (27), the pressure determined is not true capillary pressure, but that of the vessel adjacent to the tip of the cannula, i e , the arteriole or the venule Because of the structural position of the capillaries in the skin, the chances are great that the venule is adjacent to the portion of the capillary loop cannulated, thus the venous and not the capillary pressure is recorded Landis, however, in the frog by modifying the technic of Carrier and Rehberg, has avoided this objection Moreover, this method involves a distinct trauma to the tissue under study so that the pressure values can not be said to have been obtained under truly normal conditions

In our work we have employed the color blanching method for determining the capillary pressure, not because we believe that it is an ideal method, but because it is as well adapted to our purpose as any other It has the advantages of being simple and quick to employ, the technic of the procedure can not materially influence the capillaries themselves and it can be utilized over a variety of skin areas Moreover, the results observed in the normal and certain pathological states are

entirely comparative No claim is made that the values given are the absolute values for capillary pressure In the following discussion the term "capillary pressure" is used to signify the pressure necessary to cause compression of the minute subpapillary venous plexuses, and whenever reference is made to healthy or normal persons we imply people with normal cardiovascular systems

THE PROBLEM

Lewis (28) has extensively investigated the reactions of the skin vessels He has found that when the vessels are subjected to any of various stimuli, in particular to stroking or to the injection of minute amounts of histamine, there results a three-fold response First there is a local dilatation of the capillaries, then there is a fainter but much more widespread flare or flush, and lastly a local wheal Lewis attributes this response to a liberation in the skin of a substance, the action of which is identical with histamine and, therefore, is called by him H substance He has shown that the surrounding flare is due to an arteriolar dilatation, for it does not occur if the arterial blood supply is shut off This flare is the result of an axone reflex, for it also ceases to appear if the sensory nerves in the skin area in question have degenerated

In a recent article Lewis and Haynal (29) have reported studies concerning the pressure in the minute vessels of such a flare by means of small modified von Recklinghausen capsules They found the pressure to lie between 50 and 60 mm of mercury in normal individuals Krogh and Rehberg (16) also have studied this problem, using a similar method, and have obtained values of 6 to 11 cm of water (5 to 8 mm of mercury) in the same areas The cause of a difference of about 50 mm of mercury in the results lies in the criteria employed Krogh and Rehberg determined the pressure necessary to produce the first distinct blanching Lewis and Haynal on the other hand, measured the pressure necessary for the skin color to pale to that of the surrounding normal skin They showed that this is the correct criterion to employ because it is necessary to take a definite end point, which is the color of the surrounding normal skin Experimental demonstration supports this contention

If Lewis and Haynal's conception is correct, and our work tends to

confirm their idea, the minute vessels relax passively when they are congested as the result of the arteriolar dilatation in the histamine flare If they dilated actively, the pressure in them would be of a much lower order of magnitude, which seems not to be the case

The purpose of the present investigation was to make comparative studies of the capillary and arteriolar pressures (*a*) in normal people, (*b*) in patients with "essential" arterial hypertension, and (*c*) in patients with senile arteriosclerosis but with a normal blood pressure For the evaluation of the results obtained in the pathological conditions a control group of subjects to which the same technic had been applied seemed essential ' The cases with arterial hypertension were all of the so-called essential type, without signs of cardiac or renal failure at the time of the test A few of the patients complained of slight dyspnea, and some showed mild renal disease Occasionally evidence of peripheral arteriosclerosis was present

The other group of patients, those with primary senile arteriosclerosis, but with normal arterial blood pressure, was selected in order to compare the pressure in their small vessels with that of the subjects with hypertension Such a comparison may throw light on the much mooted question of the etiological and pathological relationship of arteriosclerosis and hypertension

RESULTS

The method employed by us to determine the capillary pressure was essentially the same as that used by Lewis and Haynal (29) For a detailed description of the apparatus the reader is referred to their article Both open and closed capsules were used These capsules were in the form of brass rings of five centimeters diameter, and one centimeter depth A circular piece of glass was cemented into the top, and two small brass tubes led into the sides The open capsule was sealed to the skin by a rim of thin celloidin The face of the other was covered by a membrane of goldbeaters skin, made transparent by immersion in glycerine Any desired pressure could be thrown suddenly into the capsules from a large pressure bottle, connected with mercury and water manometers The site chosen for the estimation of the capillary pressure was always the same, the skin over the manubrium and adjoining chest wall This site was selected for the follow-

ing reasons (1) With the subject prone, this area has a constant relation to the level of the heart, and is, in fact, essentially the same as that level, thus any influence of hydrostatic pressure is completely eliminated (2) This region is normally unexposed, and the vessels therein are not chronically subjected to the external influences which may affect the vessels in the face and hands (3) The vessels over the chest, usually respond with a marked flare to the injection of histamine

TABLE 1

Comparison of pressure values obtained with the open and closed capsules

Number*	Capillary pressure			Arteriolar pressure		
	Open capsule	Closed capsule	Average	Open capsule	Closed capsule	Average
	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm Hg	mm Hg
1	6	15	11	59	50	55
2	6	6	6	55	50	53
3	8	6	7	40	40	40
4	12	12	12	50	55	53
5	9	8	9	50	55	53
6	9	9	9		60	
7	4	6	5	17	16	17
8	11	16	13	33	48	40
9	16	26	21	40	40	40
10	9	9	9	40	40	40
11	12	14	13	60	60	60
12	11	11	11	50	30	40
13	16	11	13	60	70	65
14	12	14	13	45	70	58
15	11	16	13	40	45	43
16	11	10	11		65	
17	17	17	17	40	40	40
18	14	15	14	40	45	43

* 1–6, normal subjects, 7–18 arteriosclerotic subjects.

(4) This region offers the most nearly plane surface of the body, thus enabling the open capsule to be sealed to the skin easily, and provides an underlying bony resistance which is a prerequisite for the proper application of the closed capsule

Observations with both capsules were made in almost all cases, and the results obtained were in fair agreement (table 1) The values given in the other tables are an average of those obtained with the two cap-

sules whenever both methods were employed Many of the observations were made by both of the authors together, and after some practice, the values obtained by each of the two observers were in close accord The procedure of an observation was as follows First there was determined the pressure necessary to cause the minimal distinct blanching in the normal skin This criterion for capillary pressure measurement seems the most accurate, since it estimates the pressure necessary to compress the least protected and most superficial of the minute vessels of the skin, in other words, those nearest to the capillaries themselves

A local dilatation of the arterioles in the skin was next produced by the formation of a flare resulting from the pricking in of a minute amount of a 1 1000 solution of histamine phosphate As stated previously, this flare is the result of an arteriolar dilatation and therefore *the pressure in the capillaries at this time must be nearly as high* as normally exists at the commencement of the arteriolar circuit This pressure was measured by throwing into the capsules an external pressure sufficient to blanch the skin to the color of the normal surrounding skin Lewis and Haynal (29) have demonstrated that this is the valid criterion to apply Thus the capillary and the arteriolar pressures have been successively measured in the same subject

The brachial arterial blood pressure was estimated at the same time as the above measurements were made The usual Riva-Rocci technic (38) was employed The venous pressure, when measured, was determined with the method of Moritz and Tabora (30)

1 Capillary pressure

The capillary pressure values, obtained for each of the three groups of subjects, are presented in tables 2, 3, and 4, and in chart 1 Measurements are given for 10 normal persons, for 13 patients with arteriosclerosis, and for 23 patients with essential hypertension The average capillary pressure for each of the three groups is as follows normal 9 mm of mercury, arteriosclerosis 13 mm of mercury, hypertension 12 mm of mercury The close agreement between these three average figures is evident, although the capillary pressures in the pathological states appear to be slightly but definitely above normal The higher capillary pressure may in part be explained by the techni-

TABLE 2

Brachial, arteriolar and capillary blood pressures in control subjects

Number	Age	Diagnosis	Brachial blood pressure		Arteriolar pressure	Capillary pressure
			Systolic	Diastolic		
			mm. Hg	mm. Hg	mm. Hg	mm. Hg
1	14	Post rheumatic fever	128	64	55	11
2	29	No disease	124	80	63	
3	26	No disease	118	68	46	6
4	21	Convalescent pneumonia	128	64	53	6
5	23	No disease	108	65	65	8
6	45	Peptic ulcer	130	90	55	12
7	26	No disease	115	70	65	6
8	15	Diabetes mellitus	108	75	40	7
9	34	Peptic ulcer	124	78	53	12
10	14	Furunculosis	108	60	53	9
11	36	No disease	130	80	60	9
Average	26		121	72	55	9

TABLE 3

Brachial arteriolar, capillary and venous blood pressures in subjects with arteriosclerosis

Number	Age	Diagnosis	Brachial blood pressure		Arteriolar pressure	Capillary pressure	Venous pressure
			Systolic	Diastolic			
			mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg
1	58	Arteriosclerosis +++	124	86	17	5	
2	67	Arteriosclerosis +	105	45	40	13	+4
3	82	Arteriosclerosis +++	145	80	40	21	+2
4	73	Arteriosclerosis ++	145	100	40	9	+1
5	68	Arteriosclerosis ++ Post-cardiac decompensation	120	75	50	16	+3
6	73	Arteriosclerosis + Chronic myocarditis	118	80	60	13	+1
7	75	Arteriosclerosis ++	150	95	40	11	+2
8	70	Arteriosclerosis +++	149	80	65	13	+2
9	82	Arteriosclerosis +++ Cerebral accident	148	84	58	13	+5
10	66	Arteriosclerosis ++	110	70	70	—	−1
11	74	Arteriosclerosis ++	142	80	47	—	0
12	65	Arteriosclerosis +++	140	90	43	13	
13	54	Arteriosclerosis ++	124	80	65	11	
14	75	Arteriosclerosis ++ Herpes zoster	130	90	40	17	
15	73	Arteriosclerosis +++	135	70	43	14	−3
Average	70		132	80	48	13	+2

TABLE 4

Brachial, arteriolar, capillary and venous blood pressures in subjects with hypertension

Number	Age	Diagnosis	Brachial blood pressure		Arteriolar pressure	Capillary pressure	Venous pressure
			Systolic	Diastolic			
			mm Hg	*mm Hg*	*mm Hg*	*mm Hg*	*mm Hg*
1	49	Hypertension	206	114	150+	8	+3
2	47	Hypertension	170	96	75	11	
3	57	Hypertension Arteriosclerosis +	158	110	120	7	+5
4	55	Hypertension Arteriosclerosis +	214	140	165	14	+6
5	60	Hypertension Arteriosclerosis +	170	110	125	8	
6	70	Hypertension Arteriosclerosis +++	195	75	60	20	+3
7	68	Hypertension Arteriosclerosis ++	170	75	60	13	+3
8	52	Hypertension	230	145	140+	6	+3
9	52	Hypertension Arteriosclerosis ++	184	118	100	14	+5
10	65	Hypertension Arteriosclerosis ++	205	105	80	15	+2
11	55	Hypertension Arteriosclerosis ++	185	105	70	9	+3
12	68	Hypertension Arteriosclerosis +++	280	150	60	9	+3
13	60	Hypertension	190	80	80	13	
14	55	Hypertension	180	124	100	12	+4
15	17	Hypertension	180	124	100	11	+8
16	72	Hypertension Arteriosclerosis +	175	120	110	15	+3
17	77	Hypertension Heart block—complete	270	65	130	9	+7
18	41	Hypertension	180	120	150	12	+5
19	41	Hypertension	280	160	150+	10	+9
20	52	Hypertension	160	80	130	14	
21	28	Hypertension	210	130	90	21	+4
22	41	Hypertension	160	90	110	13	+6
23	31	Malignant hypertension	230	120	130	11	
Average	53		200	111	108	12	+5

cal difficulty of estimating slight degrees of skin color change in the patients of the two abnormal groups, which consisted largely of sub-

jects whose skins tended to be pale, dry and wrinkled, whereas the normal individuals were as a rule younger with firm skins of a relatively high color It can be stated, however, that the capillary pressures of normal persons, of patients with arteriosclerosis, and of subjects with hypertension, are of the same order of magnitude The capillary pressure, therefore, is essentially normal in the two pathological conditions studied

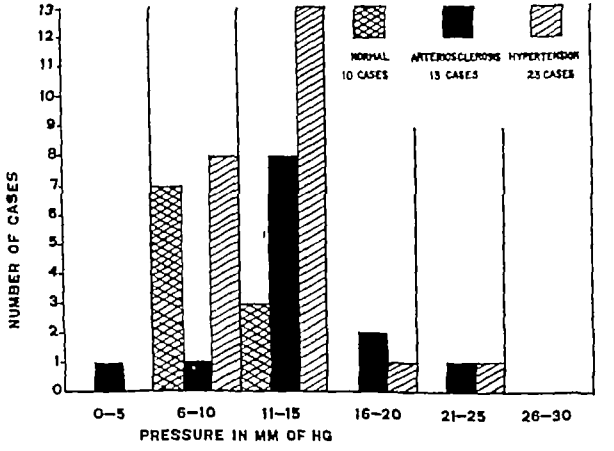

CHART 11 COMPARATIVE DISTRIBUTION OF CAPILLARY PRESSURES IN PERSONS WITH NORMAL CARDIOVASCULAR SYSTEMS AND IN SUBJECTS WITH ARTERIAL HYPERTENSION AND WITH ARTERIOSCLEROSIS

2 Arteriolar pressure

When we consider the comparative values for arteriolar pressure, obtained in vessels within a skin area in which a histamine flare has been produced, quite a different situation is found The data is presented in tables 2, 3, and 4 and chart 2 The total number of cases studied is as follows normal, 11, arteriosclerosis, 15, hypertension, 23 The average values for the normal subjects and those with senile arteriosclerosis are essentially the same, 55 and 48 mm of mercury respec-

tively In hypertension, however, the average measurement for arteriolar pressure is 108 mm of mercury, or about 100 per cent higher than in the other two groups The significance of this distinctly abnormal finding will be discussed presently

3 *Venous pressure*

The venous pressure in every case in which it was determined falls within normal limits It is less than 10 mm of mercury, and the average value is 3 mm of mercury

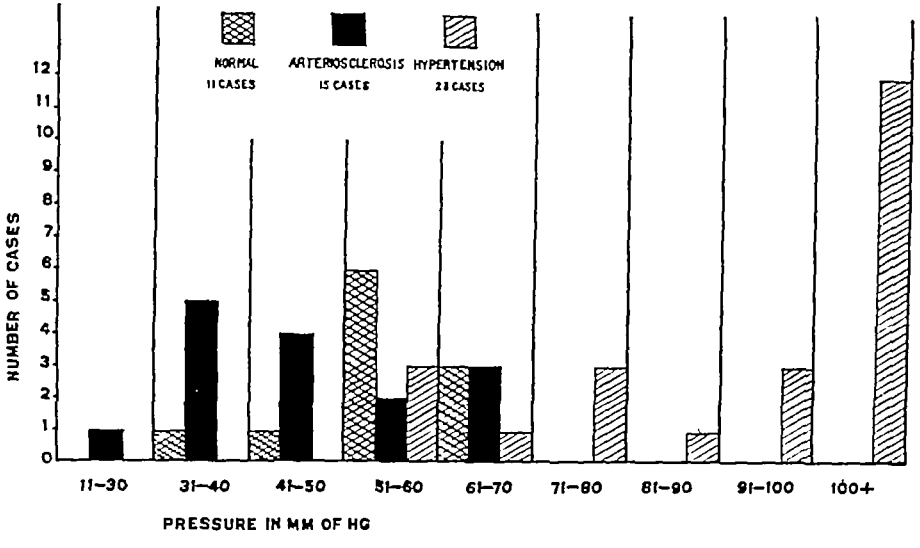

CHART 2 COMPARATIVE DISTRIBUTION OF ARTERIOLAR PRESSURE IN PERSONS WITH NORMAL CARDIOVASCULAR SYSTEMS AND IN SUBJECTS WITH ARTERIAL HYPERTENSION AND WITH ARTERIOSCLEROSIS

DISCUSSION

The values for normal capillary pressure which have been reported in the literature range all the way from 70 mm of mercury to 4 mm of mercury The higher figures undoubtedly depend on the fact that the arteriolar, not the capillary pressure was measured, while the lower figures approach that of the venous pressure It is probable that many values reported for capillary pressure have actually been for estimations of pressure in other portions of the vascular circuit The

values which we and other recent investigators have found for capillary pressure in normal individuals range from 6 to 12 mm of mercury

There are only a few reports in the literature of the measurement of capillary pressure in hypertension Basler (11) using the skin blanching method and Kylin (22), using the technic of microscopic examination, conclude that, in essential hypertension the capillary blood pressure is normal Kylin's values for the pressure, in both the normal and hypertensive states, lie between 80 and 200 mm of water (6–15 mm of mercury) Boas and Frant (31), and Boas and Mufson (32), employing essentially the same technic, found that the capillary pressure may be high or low in patients with cardiovascular disease The patients with the two types of pressure are indistinguishable clinically

For a proper comprehension of the significance of the capillary and arteriolar pressures it is essential to understand the nature of the fall of blood pressure in the arterial circuit from the great vessels to the capillaries A considerable amount of work has been done upon these pressure relationships in vessels of different caliber both in man and in animals Many results have been reported for blood pressure determinations in arteries of medium to large size, and these are not always in agreement and in certain instances appear paradoxical In general, however, the results reported are similar to those of Volkmann (33), Hürthle (34), and Dawson (35) These workers, who studied the pressures in medium and large arteries in dogs, found that the arterial pressures in the vessels under consideration varied by only a few millimeters of mercury

It has long been known that, in man, the pressure in the femoral artery may exceed considerably that in the brachial artery Gladstone (36) has considered this phenomenon at length and has offered an explanation for it His conception is that, whereas in the brachial artery only the pressure head of the blood stream is measured, in the femoral artery, which is continuous and in line with the aorta, not only is the pressure head measured, but also the velocity head, which creates an added increment to the pressure due to the velocity of the blood itself This added pressure produced by the velocity of the blood stream is a feature peculiar to the femoral artery and does not obtain in the other and smaller arteries It may be concluded that there is a slight fall of pressure as the blood passes through the large

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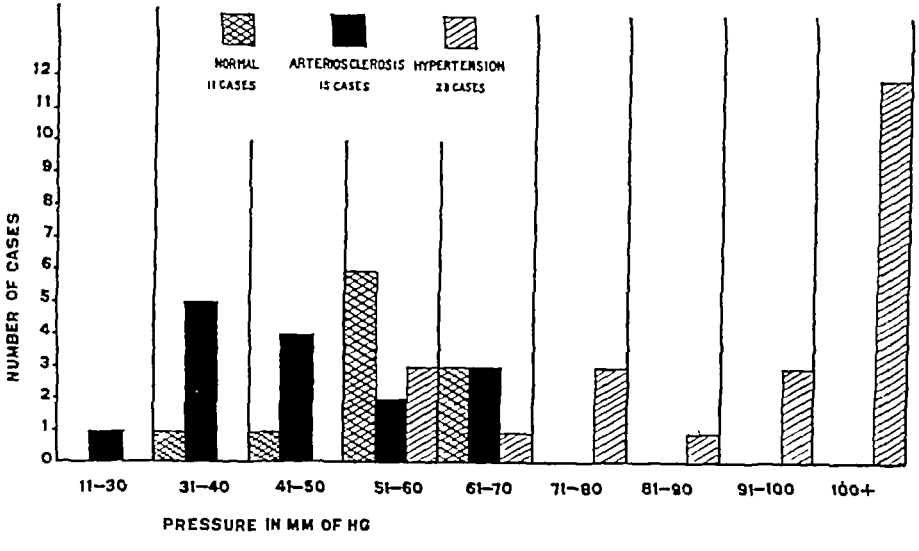

CHART 2 COMPARATIVE DISTRIBUTION OF ARTERIOLAR PRESSURE IN PERSONS WITH NORMAL CARDIOVASCULAR SYSTEMS AND IN SUBJECTS WITH ARTERIAL HYPERTENSION AND WITH ARTERIOSCLEROSIS

DISCUSSION

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3 and 4 The pressure then falls rapidly to the normal value in the veins

When the same curve for the pressures of hypertensive patients is considered (chart 3) it is found to vary in its contour from the normal The mean brachial pressure is, of course, distinctly higher, in our

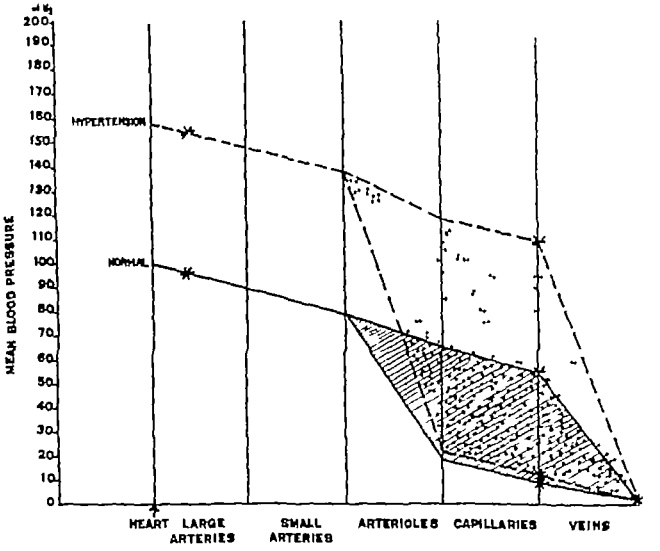

CHART 3 DIAGRAMMATIC REPRESENTATION OF FALL IN BLOOD PRESSURE IN VASCULAR CIRCUIT IN SUBJECTS WITH HYPERTENSION COMPARED WITH THE NORMAL

Shaded and stippled areas represent alteration in the pressure relationships in the skin vessels after the injection of histamine The lower boundaries of these areas represent the pressure gradient under natural conditions the upper boundaries this gradient after the injection of histamine

cases being 155 mm of mercury The capillary pressure, on the other hand, is of essentially the same order of magnitude as in the normal patients, 12 mm of mercury There must be, therefore, a distinctly greater fall in the arterial circuit than in normal subjects There is

and medium-sized arteries, but that this fall rarely, if ever, exceeds 20 mm of mercury

Few reports are available dealing with the fall of pressure between the medium-sized arteries and the arterioles It is safe to assume that there is a moderate fall here, but from a consideration of the total diameter and length of these vesssels, there is no reason to believe that there is any important drop in the blood pressure

There has been a controversy among physiologists as to whether the chief point of resistance in the vascular circuit lies in the arterioles or the capillaries The earlier belief was that the capillaries themselves offer the greatest resistance and that the drop in pressure is most marked here More recently, however, it is generally accepted that the blood pressure falls markedly in the arterioles (precapillaries), due to the resistance existing here, and therefore the pressure in the capillaries would tend to approach that in the veins In the main, the many observations on capillary pressures tend to confirm this view

In the accompanying diagrams (charts 3 and 4), there is a schematic representation of the fall of blood pressure from the large arteries to the veins in normal individuals and patients with hypertension and arteriosclerosis The values are an average of the individual measurements in each group The stars represent points in the vascular circuit at which actual measurements were made, namely, the brachial, capillary and venous blood pressures

Under natural conditions, in normal individuals, there is a slight drop of pressure in the large and small arteries from the mean brachial pressure of 96 mm of mercury The total fall in these vessels is probably not greater than 20 mm of mercury When the arterioles are reached there is a marked fall of pressure due to the increased resistance interposed here In the capillaries of the normal subjects studied the average pressure is 9 mm of mercury That the most striking drop of pressure actually does take place in the arterioles is confirmed by the findings after the production of a histamine flare Under such circumstances the arterioles are dilated, thus diminishing the resistance, so that the pressure in the capillaries at once becomes nearly as high as in the arterioles, and was found in our cases to average 55 mm of mercury This change in the pressure gradient following histamine injection is diagramatically represented in the shaded area of charts

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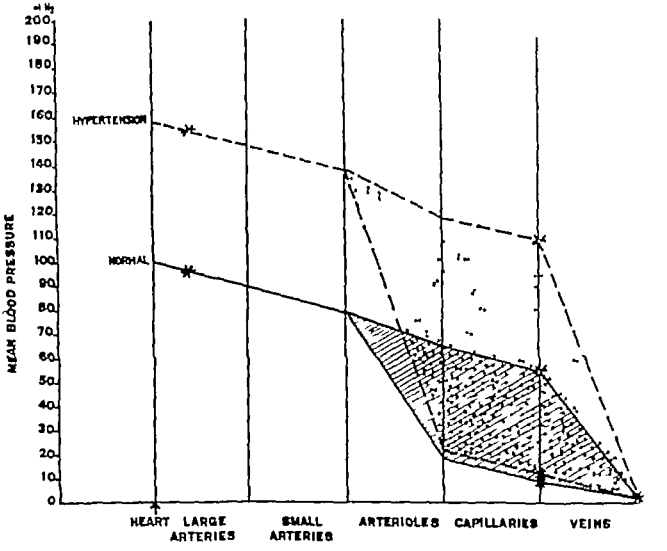

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no reason to believe that in essential hypertension the resistance interposed by the arteries themselves is markedly greater than under normal conditions The increased resistance in hypertension must accordingly be in the arteriolar portion of the circuit so that the fall in pressure occurs here In arterial hypertension when the arteriolar

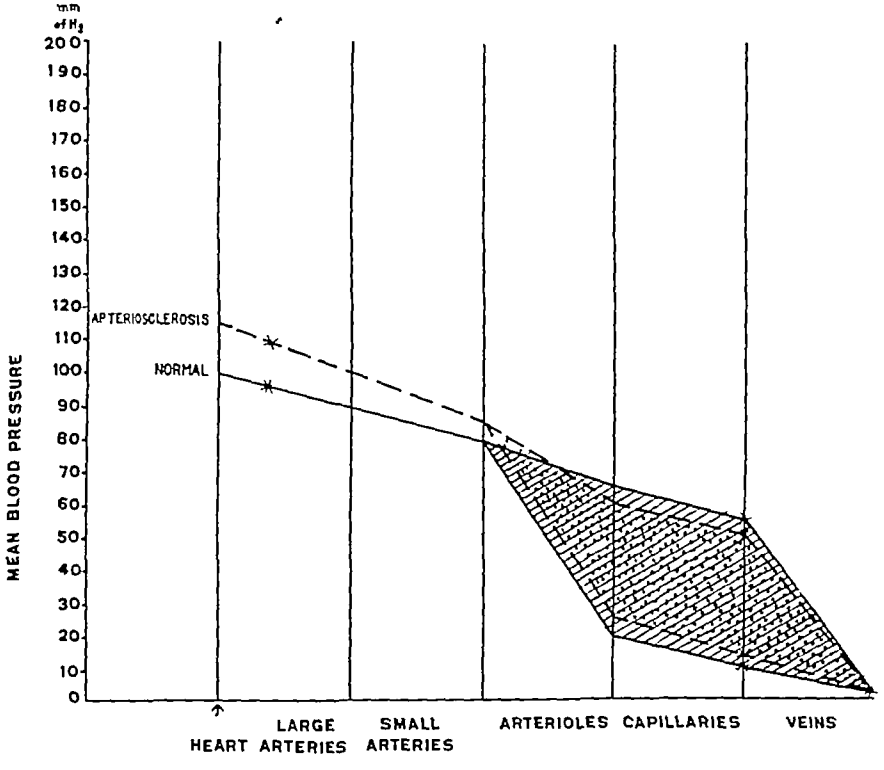

CHART 4 DIAGRAMMATIC REPRESENTATION OF FALL IN BLOOD PRESSURE IN VASCULAR CIRCUIT IN SUBJECTS WITH ARTERIOSCLEROSIS COMPARED WITH THE NORMAL

Shaded and stippled areas represent alteration in pressure relationships in the skin vessels after the injection of histamine The lower boundaries of these areas represent the pressure gradient under natural conditions, the upper boundaries this gradient after the injection of histamine

pressure in vessels dilated with histamine was determined, it was found to be on the average 108 mm of mercury, or twice as high as in the normal individuals The increase above normal is, in fact, approximately of the same order of magnitude as the increase of

brachial mean blood pressure From this important fact several conclusions can be drawn First, the chief resistance in the arterial circuit in hypertension lies in the same portion of the circuit as in health, but is of much greater magnitude Second, this resistance, in the arterioles of the skin at least, is partly of a functional and not an organic character, because it can be overcome by a reflex induced by the injection of histamine, when the raised arterial pressure is transmitted into the capillaries

Since the capillary pressure in arterial hypertension is normal, and there exists a definitely increased resistance in the arterioles, it is suggested that the hypertension is a compensatory mechanism on the part of the human organism to maintain a normal capillary blood pressure If no hypertension existed, the fall in pressure in the arterioles would be so great that the capillary pressure would be far below normal, the exchange of gases with the tissues would be seriously interfered with, and bodily functions would be markedly hampered

The curve for the average pressure of the arteriosclerotic group of patients is similar to that for normals (chart 4) It can, therefore, be concluded that arteriosclerosis, per se, does not necessarily interfere with normal capillary pressure nor does it produce a greatly increased resistance in the arterioles Indeed, the fact that the arteriolar pressure, in proportion to that in the brachial artery is somewhat lower than in normal persons, is evidence that the resistance in arteriosclerosis is increased relatively in the larger vessels and not in the arterioles Histological observations are often in accord with this

The 23 patients with arterial hypertension may be divided into two groups, one comprising seventeen patients with either no or slight clinical evidence of arteriosclerosis, and the other including six patients with distinct or marked arteriosclerosis One finds that the average arteriolar pressure of the first group is 121 mm of mercury, and of the second group is 71 mm of mercury The average capillary pressure, however, is about the same in each group The reason for the relatively low value for arteriolar pressure in the second group with marked arteriosclerosis may be dependent upon the fact that either (*a*) the mean pressure drops to a considerable degree before the arteriolar system is reached as a result of organic changes in the large arteries, or (*b*) the true pressure in the arterioles is actually of the same height

in both groups, but because of the presence of arteriosclerosis, the arterioles can not respond to histamine as extensively with a functional dilatation as in the group where there is little or no organic narrowing of these vessels The clinical behavior of these patients favors this second explanation

The observation that the pressure in the capillary system when the arterioles are under the effect of histamine is higher than normal in patients with hypertension suggests that under certain physiological conditions demanding increased blood supply, such individuals with hypertension have a greater capacity to respond with increased localized blood flow than do normal persons According to chart 4, patients with senile arteriosclerosis and a normal blood pressure tend to have less capacity than normal individuals to respond to the same demand

The difference between the pressure gradient curve obtained in senile arteriosclerosis with normal arterial blood pressure and that in hypertension without arteriosclerosis is striking, and is evidence toward the belief that senile, nodular arteriosclerosis, and essential hypertension are two distinct entities, although, as is so often the case, they may exist coincidentally

SUMMARY

1 A study is presented of the brachial, arteriolar, and capillary blood pressures in three groups of individuals (1) persons with normal cardiovascular systems, (2) patients with arterial hypertension, and (3) patients with senile, nodular arteriosclerosis

2 The capillary pressures in these three groups are of the same order of magnitude The average capillary pressure in normal subjects is 9 mm of mercury, that of patients with hypertension 12 mm of mercury, and in patients with senile arteriosclerosis 13 mm of mercury

3 The arteriolar pressure in arteriosclerosis is normal, but is greatly increased in arterial hypertension The average arteriolar pressure in normal subjects is 55 mm of mercury, that of patients with arterial hypertension 108 mm of mercury, and in patients with senile arteriosclerosis 48 mm of mercury

4 The chief resistance in the vascular circuit normally lies in the arteriolar (precapillary) portion of the vessels

5 Hypertension is due to an increased resistance in the vascular

circuit Evidence is presented that this resistance lies in the arteriolar portion, as in normal persons, and in the absence of marked arteriosclerosis, is functional in character Hypertension may be a compensatory phenomenon designed to maintain normal tissue oxidation through a normal capillary blood flow

6 Evidence for the basic difference between arterial hypertension and senile arteriosclerosis is given

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THE ENDOGENOUS URIC ACID METABOLISM IN PERNICIOUS ANEMIA

By MATTHEW C RIDDLE[1]

(From the Thomas Henry Simpson Memorial Institute for Medical Research, University of Michigan, Ann Arbor)

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The investigations of Rosenquist (1) and of Gibson and Howard (2) on the urinary excretion of endogenous uric acid and of Gettler and Lindeman (3) on the uric acid content of the blood in pernicious anemia suggest a disturbance of the purine metabolism in this disease. The results of these studies are characterized by their variability and by the frequency of abnormally high values for uric acid in the blood and urine of patients with pernicious anemia

These investigations were performed before the discovery by Minot, Murphy, Cohn and their associates (4) (5) (6) (7) (8) of the specific therapeutic effect of liver and of extracts of liver in pernicious anemia The remarkable improvement in patients following the daily ingestion of small amounts of liver extract suggests an association of the disease process with some unknown disorder of metabolism and indicates the importance of a reëxamination and reëvaluation of the existing knowledge of the metabolic manifestations of this disease

Fortunately liver and liver extract, aside from their remedial value, provide a method for the experimental control of the course of the disease Remissions may be produced at will and consequently may be anticipated for experimental purposes This paper deals with the behavior of the endogenous uric acid metabolism during the early stages of remission in patients with pernicious anemia

MATERIAL AND METHODS

The endogenous uric acid metabolism was studied over periods of ten to seventy-four days in twelve patients, eight men and four women,

[1] Fellow in Medicine of the National Research Council

and in one normal person, the latter serving as a control Each patient exhibited the characteristic blood findings, symptoms and response to liver extract therapy which occur in pernicious anemia In all patients free hydrochloric acid was absent from the gastric contents None of these patients had used liver or liver extract recently enough or in sufficient quantities to modify the course of the disease, so all were observed during a relapse except one woman, who was seen first very early in a spontaneous remission

Before treatment four of the twelve patients had red blood cell counts of less than 1,000,000 per cubic millimeter, six had counts between 1,000,000 and 1,500,000, and two had counts between 1,500,000 and 2,500,000 Of the twelve, six were in their first relapse, four in the second and one was in a fifth and one in a seventh relapse

In each patient the various dietary constituents and the total caloric intake were known and recorded each day To avoid exogenous sources of uric acid, purine-poor diets were used, from which foods containing nucleic acid compounds or purine derivatives such as meats, fish, peas, beans, tea, coffee and chocolate were excluded The diets were otherwise limited only by the patient's appetite

In general the use of drugs was avoided to prevent variations in uric acid excretion from this source although dilute hydrochloric acid was given to two patients in amounts of 12 0 cc daily without apparent influence on the uric acid metabolism

Estimations of the amount of uric acid excreted each 24 hours in the urine were made throughout each period of observation Frequent estimations of the uric acid content of the blood serum of fasting individuals were also made, in most patients every day Serum rather than whole blood was used for this purpose to avoid the effect of the variation in the number of red blood cells since uric acid is distributed unequally between serum and cells

In most patients, the daily excretion of other urinary constituents was determined In all patients except one, the creatinine excretion was determined daily, since, being relatively constant in amount in the urine from day to day, creatinine serves as an index of accuracy of urine collection In some patients, the daily urinary excretion of total nitrogen, urea nitrogen and ammonia nitrogen was studied In others only the amount of total nitrogen excretion was determined

The method of Folin and Wu (9) (10) was used in urine uric acid determinations The direct method of Folin-Benedict (10) (11) was employed in the determination of uric acid in the blood serum Folin's method (10) (12) was used in the estimation of creatinine in the urine The colorimetric methods (10) (13) (14) (15) (16) of Folin, using the modified Nessler-Winkler reagent, were employed for the estimation of total nitrogen, urea nitrogen and ammonia nitrogen in the urine

The cellular changes in the blood were carefully followed in each patient with daily determinations of the percentage of the reticulocytes and frequent estimations of the numbers of red and white blood cells and of the amount of hemoglobin (Sahli method) in the blood

In all laboratory procedures the usual precautions were observed to insure accuracy

Before treatment, each patient was usually studied for a period of one to five days to observe the character of the endogenous uric acid metabolism during relapse Then liver extract[2] was given, usually in doses of six vials daily (equivalent to 600 grams of liver) This experimental procedure was occasionally modified to demonstrate special features of the uric acid metabolism, which are discussed elsewhere The data thus accumulated are too numerous to present in detail Consequently, except when charts or tables are used to illustrate certain important points, the results are generally summarized

THE URIC ACID METABOLISM DURING RELAPSE

With the method of estimation used (10) (11), the amount of uric acid found in 25 determinations on the blood serum of normal fasting persons varied from 3 3 to 4 7 mgm per 100 cc of serum, the average value being 3 9 mgm per 100 cc

The amount of uric acid in the blood serum of eleven fasting patients with pernicious anemia, is shown in table 1 These determinations were made during a relapse, before treatment was given and while the patients were using a purine-poor diet Uric acid was present in less

[2] Commercial liver extracts were used, Lilly's Liver Extract No 343 or Parke-Davis Liver Extract except in two patients who were given a liquid extract of cod livers, manufactured by White Laboratories, Inc , Gloucester, Mass A vial of liver extract represents 100 grams of fresh liver

than the normal concentration in the blood serum of six patients under these circumstances, in normal concentration in three patients, and in a concentration greater than normal in only two patients In the patient who showed the greatest amount of uric acid in the blood serum, 12 5 mgm per 100 cc of serum, chronic nephritis was present which may explain the uric acid retention observed In the other patient with an increased serum uric acid value, 7 1 mgm per 100 cc of serum, hyperthyroidism was present, the basal metabolic rate being +47, and for a period of three days the patient was ill with an upper respiratory infection, his buccal temperature rising as high as 103 2°F.

TABLE 1

Blood serum uric acid values in pernicious anemia before treatment

Milligrams of uric acid per 100 cc of blood serum

High values (2 patients)	12 5 4 6–7 1
Normal values (3 patients)	4 2–5 0 4 3–5 1 4 3–4 9
Low values (6 patients)	2 4–2 8 2 4–2 7 2 5–2 7 2 8 1 9–2 8 1 6–2 2

During the febrile period the elevated serum uric acid figure of 7 1 mgm per 100 cc was obtained Before this febrile disturbance serum uric acid values were within normal limits, being 4 6 mgm per 100 cc Also it is interesting to observe that, during the febrile period, this patient excreted abnormally large amounts of uric acid in the urine, 846 and 1488 mgm of uric acid in two of the 24 hour periods During other days the uric acid excretion was less than 600 mgm per day Figure 3 shows the findings on this patient

With this one exception the daily urinary excretion of endogenous uric acid, in all patients on a purine-poor diet studied before treatment was essentially normal, the daily excretion varying between 164 and

667 mgm of uric acid The amount of endogenous uric acid excreted normally each day is considered generally to vary between 200 and 600 mgm In the normal person used as a control in this study, the daily excretion of endogenous uric acid, when liver extract was not given, was between 385 and 522 mgm

From the analysis of these figures representing the endogenous uric acid excretion during relapse, no obvious abnormality of uric acid excretion appears to be present before treatment In the case mentioned above, the increased excretion of uric acid was supposedly a result of hyperthyroidism and fever

The amounts of uric acid in the blood serum were usually normal or less than normal before treatment In only two cases were high values obtained and, in one of these, the factors of hyperthyroidism and fever were present, which probably augmented the amount of uric acid in the serum, and in the other chronic nephritis was present

These results cannot be compared directly to those of Rosenquist (1), Gibson and Howard (2), and Gettler and Lindeman (3) who found the uric acid metabolism usually increased in pernicious anemia, since these investigators did not limit their observations to the period of complete relapse

THE URIC ACID METABOLISM DURING REMISSION

A prompt and satisfactory response to liver extract treatment was observed in every patient This was manifested in each case by the typical rise and fall in the percentage of reticulocytes during the first two weeks of treatment, by the steady increase in the numbers of red and white blood cells, and by the rapid clinical improvement which accompanies a remission in pernicious anemia The remission was satisfactory in the two patients receiving cod liver extract, but was longer delayed than in the patients who were given the more effective liver extracts

Very definite changes in the endogenous uric acid metabolism accompanied a remission in every patient The response of the uric acid metabolism to liver extract treatment was characterized by an increased excretion of uric acid in the urine and by an increase in the concentration of uric acid in the blood serum The response of the uric acid metabolism to treatment may be divided conveniently into

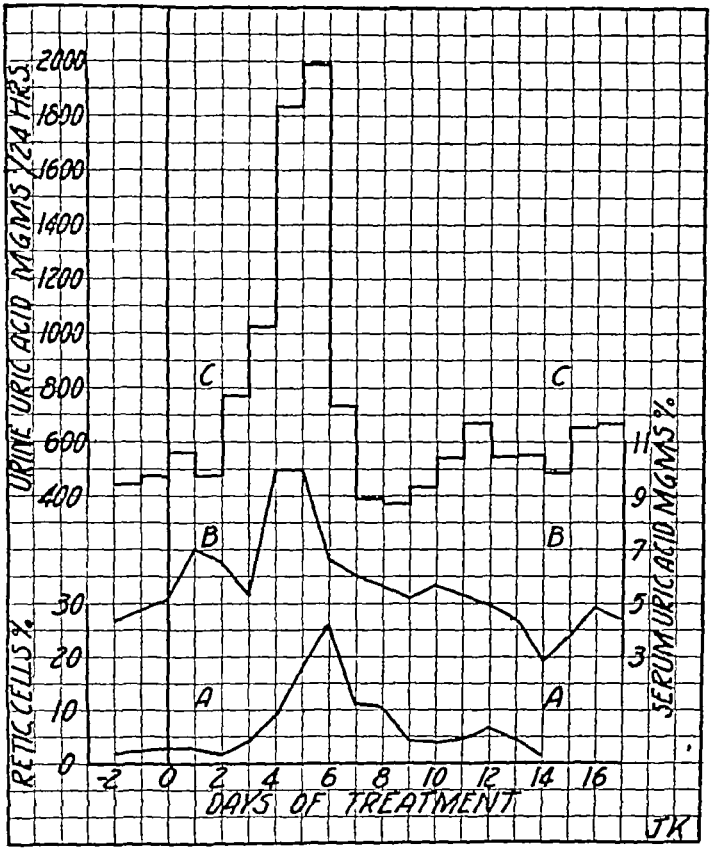


FIG 1 URIC ACID METABOLISM AND RETICULOCYTE PERCENTAGE DURING EARLY REMISSION

Patient J K Before treatment red blood cells 1,070,000 Hemoglobin 22 per cent (Sahli) On the 18th day of treatment red blood cells 3,460,000 Hemoglobin 50 per cent (Sahli)

Treatment 6 vials liver extract daily Lilly's liver extract, No 343 0–4th day Parke-Davis liver extract 4–17th day Beginning of treatment is indicated by the vertical line

A = percentage of reticulocytes

B = concentration of uric acid in fasting blood serum in milligrams of uric acid per 100 cc

C = urinary uric acid excretion in milligrams of uric acid per 24 hours

two phases The first phase includes the first two weeks of treatment, during which the rise and fall in the percentage of reticulocytes occurs It is characterized by a rise and fall in the amounts of uric acid in the blood serum and in the daily volumes of urine (see figs 1 and 2) The

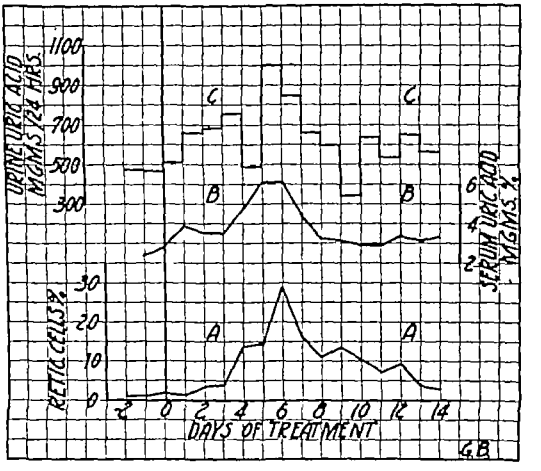


FIG 2 URIC ACID METABOLISM AND RETICULOCYTE PERCENTAGE DURING EARLY REMISSION

Patient G B Before treatment red blood cells 1,310,000 Hemoglobin 25 per cent (Sahli) On the 13th day after treatment, red blood cells 2,350,000 Hemoglobin 51 per cent (Sahli)

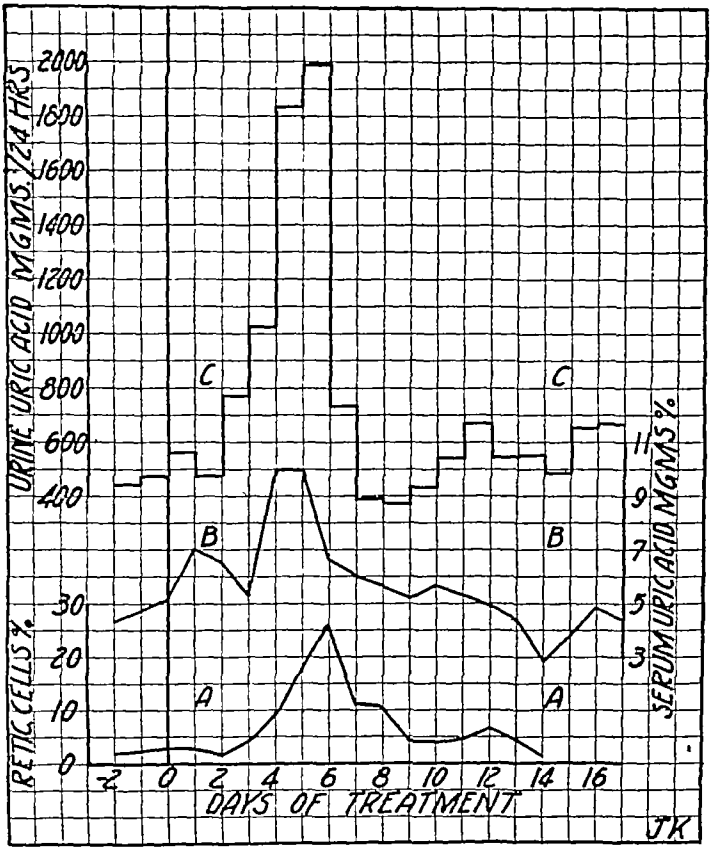
Treatment 6 vials of Lilly s liver extract No 343 daily The beginning of treatment is indicated by the vertical line

A = percentage of reticulocytes

B = concentration of uric acid in fasting blood serum in milligrams of uric acid per 100 cc.

C = urinary uric acid excretion in milligrams of uric acid per 24 hours

second phase follows the reticulocyte response and occurs during the period of rapid blood regeneration During this phase the concentration of uric acid in the blood serum and the daily excretion of uric acid rise again to an elevated level which is maintained, if liver extract



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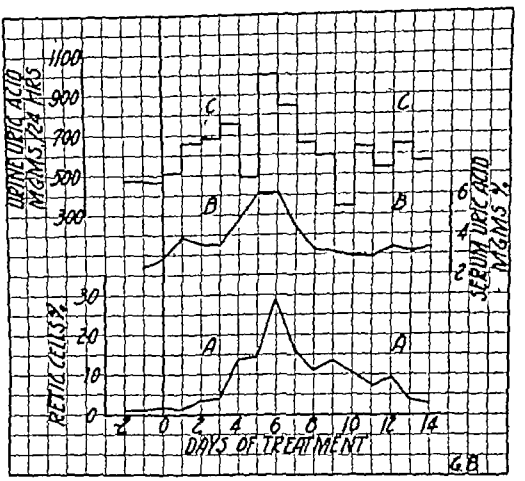

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Patient G B Before treatment red blood cells 1,310,000 Hemoglobin 25 per cent (Sahli) On the 13th day after treatment, red blood cells 2,350,000 Hemoglobin 51 per cent (Sahli)

Treatment 6 vials of Lilly's liver extract No 343 daily The beginning of treatment is indicated by the vertical line

A = percentage of reticulocytes

B = concentration of uric acid in fasting blood serum in milligrams of uric acid per 100 cc.

C = urinary uric acid excretion in milligrams of uric acid per 24 hours

second phase follows the reticulocyte response and occurs during the period of rapid blood regeneration During this phase the concentration of uric acid in the blood serum and the daily excretion of uric acid rise again to an elevated level which is maintained, if liver extract

therapy continues, for at least 60 days Observations were not made over longer periods These changes are illustrated by figure 3

The initial rise in the concentration of uric acid in the blood serum was apparent within 24 hours after liver extract was first given The

FIG 3 THE EFFECT OF LIVER EXTRACT MEDICATION ON THE URIC ACID METABOLISM

Patient G F Before treatment red blood cells 860,000 Hemoglobin 19 per cent (Sahli) On the 26th day of treatment red blood cells 3,300,000 Hemoglobin 61 per cent (Sahli) This patient in addition to pernicious anemia had hyperthyroidism and, during the three days before treatment was begun, had fever from an influenzal upper respiratory infection

Treatment Lilly's liver extract No 343, 6 vials daily from 0–17th day and from 24th–28th day

A = percentage of reticulocytes

B = concentration of uric acid in the fasting blood serum in milligrams of uric acid per 100 cc

C = urinary uric acid excretion in milligrams of uric acid per 24 hours

X = beginning of liver extract treatment

Y = liver extract treatment stopped

Z = liver extract treatment resumed

amounts of uric acid in the blood serum continued to increase for several days reaching maximal values after four to six days of treatment There was then a decrease in the concentration of uric acid in

the serum so that, at the end of fourteen days, the uric acid in the serum had returned to approximately the original amounts

A similar rise and fall in the amounts of uric acid excreted each day in the urine was found during this period A significant increase in the uric acid excretion was observed within two days, usually during the first day, following the first administration of liver extract Maximal values were obtained between the fifth and seventh days By the fourteenth day, the daily excretion of uric acid in the urine had returned to approximately its original level

Exceptions to these observations occurred in only three patients In them the same changes in the uric acid metabolism were observed but were delayed Two of these patients received the less effective cod liver extract and the reticulocyte response was also delayed In the third patient the initial red blood cell count was relatively high, being 2,490,000 before treatment

The maximum increase in the serum uric acid values during the first two weeks of treatment varied from 28 to 239 per cent The actual increase, at the maximum, varied from 1 1 to 5 5 mgm of uric acid per 100 cc of serum The maximal percentage increase in urine uric acid values varied from 74 to 531 per cent The actual increase in urinary excretion varied from 386 to 1854 mgm of uric acid per day during the days of greatest uric acid excretion These figures clearly indicate the very marked increase in the uric acid metabolism which occurs during the first two weeks of treatment

The fluctuations of the urinary uric acid excretion, of the concentration of uric acid in the serum and of the percentage of reticulocytes parallel one another closely during the first two weeks of remission Even minor secondary rises in the percentage of reticulocytes are usually accompanied by similar increases in the uric acid values for the urine and serum Close examination of the data indicates that changes in the amount of uric acid excreted in the urine are usually preceded by similar changes in the concentration of uric acid in the blood serum Likewise fluctuations in the percentage of reticulocytes are preceded by similar fluctuations in the uric acid values for urine and serum This sequence of events may be demonstrated in figure 1 Here the first increase of uric acid in the serum occurs during the first day of treatment Increased excretion of uric acid in the urine appears

between the second and third day and the first rise in the percentage of reticulocytes occurs on the third day A maximum amount of uric acid was present in the serum on the fourth day, the greatest amount of uric acid was excreted between the fifth and sixth day and the greatest percentage of reticulocyte appeared on the sixth day The appearance of the highest percentage of reticulocytes on the day following the greatest uric acid excretion is a very constant finding

Observations were terminated at the end of the first phase of the response of the uric acid metabolism in all but two patients, one patient being studied for a period of 70 days after treatment was started, the other for 28 days . The findings on the latter patient are shown (fig 3) since the results in the both cases are similar This patient had a recurrent hyperthyroidism, following an operation for exophthalmic goitre two and a half years before, and, during the period of observation preliminary to treatment suffered from an intercurrent upper respiratory infection of the influenzal type lasting three days, with fever reaching 103 2°F and a leucopenia This illness apparently caused a disturbance of the uric acid metabolism with an increase in the uric acid in the blood serum and in the urine However when this had subsided and liver extract treatment was instituted the uric acid metabolism in this patient was similar to that in other patients in every way This patient shows the increase of the uric acid metabolism during the second phase of remission and the effect of discontinuing liver extract treatment As the percentage of reticulocytes decreased the uric acid values for both urine and serum fell to their original levels but rose later when the reticulocytes had decreased to a normal percentage On the seventeenth day of treatment when liver extract was discontinued, the concentration of uric acid in the blood serum and the daily rate of uric acid excretion decreased abruptly and remained at a low level until liver extract treatment was resumed Then uric acid reappeared in increased amounts in both serum and urine During the second phase of remission, that following the reticulocyte response, although the reticulocytes were not increased in percentage, the red blood cell count rose steadily, increasing from 2,260,000 on the sixteenth day to 3,300,000 on the twenty-sixth day

The patient, whose findings are shown in table 2, showed certain

TABLE 2

Uric acid values during liver extract treatment, according to direct and indirect methods of estimation*

Patient E P

Day of treatment	Serum uric acid			Percentage of reticulocytes	Day of treatment	Urine uric acid
	Method 1	Method 2	Method 3			
	mgm per 100 cc.	*mgm. per 100 cc.*	*mgm per 100 cc*			*mgm per day*
0	12 5	12 3	11 8	4 5	0–1	562†
1	13 8	13 8	12 7	4 1	1–2	629
2	16 0	16 0	13 1	3 0	2–3	1,268
3	12 7	12 7	11 4	5 2	3–4	1 404
4	12 5	12 5	11 1	16 3	4–5	1,806
5	13 1	13 1	11 6	24 7	5–6	1 709
6	13 8	13 8	11 4	27 5	6–7	1 326
7	11 4	11 4	9 8	24 9	7–8	1 062
8	10 4	10 4	8 7	16 9	8–9	704
9	8 1		7 1	6 6	9–10	768
10	9 5	9 6	7 0	8 3	10–11	740
11	11 2	11 2	9 0	5 9	11–12	1 534
12	10 2	10 2	8 0	4 1	12–13	932
13	9 2	9 0	7 0	7 4	13–14	603
14	9 2	9 0	7 8	6 7	14–15	857
15	9 1	9 0	7 7	5 8	15–16	649
16	7 8	7 8	7 0	4 6	16–17	571
17	8 7	8 7	7 6	4 2	17–18	539
18	8 2	8 2	7 8	3 9	18–19	620
19	8 6	8 6	7 5	3 4	19–20	650
20	9 8	9 6	8 3	5 6	20–21	705
21	8 4	8 0	7 6	3 8	21–22	797
22	6 6	6 4	6 2	3 0		

* Treatment—12 vials of Lilly's liver extract No 343 per day for the first seven days of treatment The dose was then decreased to six vials daily

Methods of serum uric acid estimation

No 1 Folin Benedict direct method (10) (11)

No 2 Folin indirect method (11) using silver lactate.

No 3 Morris-MacLeod indirect method (17) using zinc sulphate

In all methods the Folin and Denis (10) (18) uric acid reagent was used to produce the color reaction

† Estimated Urine specimen incomplete.

unusual features The serum uric acid value before liver extract was given was unusually high, 12 5 mgm per 100 cc. Nevertheless there was as usual, an increase, 16 0 mgm of uric acid being present per

100 cc of blood serum after two days of treatment The decrease of uric acid in the blood after this maximal value was reached was greater in this case than in any other and, on the twenty-second day, there were only 6 6 mgm of uric acid per 100 cc of serum, which, although still more than found in normal serum was approximately half the

TABLE 3

Protein consumption, urinary nitrogen total and uric acid excretion during early remission

Day of treatment	Patient (C S)			Patient (G F)			Patient (J K)		
	Food protein	Total urine nitrogen	Urine uric acid	Food protein	Total urine nitrogen	Urine uric acid	Food protein	Total urine nitrogen	Urine uric acid
	grams per day	*grams per day*	*mgm per day*	*grams per day*	*grams per day*	*mgm per day*	*grams per day*	*grams per day (average)*	*mgm per day*
0–1	65 9	9 10	751	29 9	9 92	655	37 7		565
1–2	54 6	9 87	715	59 5	8 78	917	27 0		473
2–3	70 5	10 42	723	50 6	4 65	823	29 8	6 29*	771
3–4	66 6	8 97	758	58 7	5 00	1,459	14 9		1,016*
4–5	55 9	10 00*	418*	52 4	9 32	2,268	19 4		1,829
5–6	73 4	10 43	851	59 4	9 44	2,407	16 7		1,993*
6–7	53 9	9 17	1,075	63 1	6 99	963	31 8	4 33*	725
7–8	64 3	8 80	1,058	66 0	7 48	740	49 6		396
8–9	51 2	8 17	827	65 7	6 71	520	35 3		383
9–10	54 9	9 28	652	69 8	8 21	684	36 2		427
10–11	63 2	8 91	657	66 7	7 24	630	48 4	5 93	535
11–12	60 1	7 19	537	87 3	8 40	1,120	40 2		672
12–13	63 4	7 63	708	80 0	6 15	643	39 1		537
13–14	65 5	7 22	949	71 4	5 91	831	49 3		541
14–15	67 2	8 73	781	66 4	8 33	1,391	54 5	5 17	489
15–16	65 3	9 00	825	78 2	7 74	952	35 0		647
16–17				71 8	7 60	986	50 5		667

* Estimated Urine specimens incomplete

amount present before treatment The reason for the original high value in this patient was attributed to nephritis

The variations in the uric acid metabolism during remission were independent of the protein metabolism The amounts of protein ingested varied usually between 40 and 70 grams a day, usually tending to rise with the increase of appetite as remission advanced There was a tendency towards nitrogen retention during remission, in spite of the increased excretion of uric acid nitrogen No evident ab-

normalities of nitrogen metabolism other than that of uric acid nitrogen was observed The changes in uric acid metabolism were independent of protein intake, and urinary nitrogen excretion as is shown in table 3, where the daily protein intake, the total urinary nitrogen excretion and the excretion of uric acid is listed for three patients

Urine uric acid determinations were made by an indirect method (9) (10) using silver lactate for the isolation of uric acid A direct method for determination of the uric acid in serum was used, leaving these estimations open to the criticism that other substances than uric acid possibly were included in the values obtained To avoid this criticism, in two patients (fig 6 and table 2) the serum uric acid values were obtained by the direct method usually employed and by two indirect methods, the Folin method (11) using silver lactate and the Morris and MacLoed (17) method using zinc sulphate to isolate the uric acid in the serum for estimation The results obtained indicate the fact that the fluctuations of the uric acid values depend upon changing amounts of uric acid in the blood serum and were not due to other substances The results from the Folin methods, direct and indirect, were in close agreement The zinc sulphate method gave lower figures, as is usually the case, but showed the same fluctuations found in the other two methods

THE ENDOGENOUS CHARACTER OF THE INCREASED URIC ACID METABOLISM

Liver extract, which is known to contain considerable amounts of purine materials,[3] conceivably might serve as an exogenous source of uric acid Actually however, the purine materials in liver extract do not appear to influence the uric acid metabolism significantly That this is true is shown by the following four experiments which demonstrate that the influence of the uric acid precursors in liver extract is of no particular significance in the increased excretion of uric acid which is observed during a remission

[3] Figures on the purine nitrogen content of liver extract available through the kindness of Dr Oliver Kamm and Dr E A Sharpe of Parke Davis and Company, show that Parke Davis Liver Extract contains 5.21 per cent purine nitrogen and Lilly's Liver Extract No 343 2 71 per cent purine nitrogen

In the first experiment the effect of liver extract on the uric acid metabolism of a normal person using a purine-poor diet was studied After four days of preliminary observation, six vials of liver extract were given daily for ten days, observations being continued for three days after liver extract was discontinued The results are shown in figure 4 No significant changes in the percentage of reticulocytes, in the urinary uric acid excretion or in the concentration of uric acid

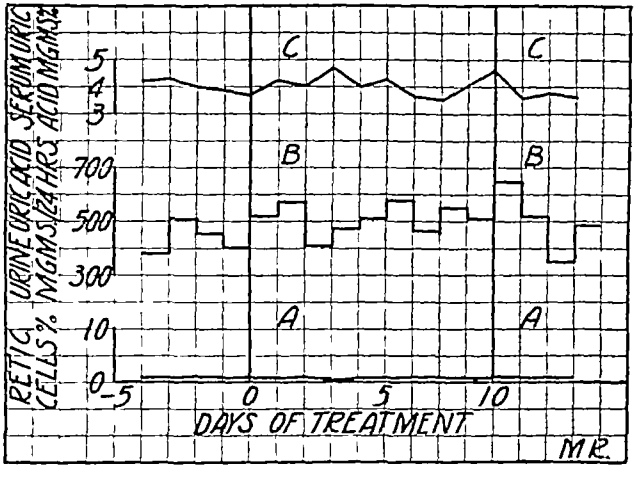

FIG 4 THE EFFECT OF LIVER EXTRACT MEDICATION ON THE URIC ACID METABOLISM IN A NORMAL PERSON

Normal person—M R

Treatment 6 vials Lilly's liver extract No 343 daily from 0–10th day Vertical lines indicate beginning and end of liver extract therapy

A = percentage of reticulocytes

B = urinary uric acid excretion in milligrams of uric acid per 24 hours

C = concentration of uric acid in fasting blood serum in milligrams of uric acid per 100 cc

in the blood serum were observed During the period of liver extract administration, the average daily excretion of uric acid exceeded that of the control periods by 79 milligrams, an amount which probably represents the increase due to the purine materials in liver extract

The results of a second experiment are shown in figure 5 Here 30 vials of liver extract were given to a patient with pernicious anemia

in a single day and no further medication was used during the experiment A satisfactory remission was produced and the changes in the uric acid metabolism were identical to those obtained in patients who received six vials of liver extract daily, as may be seen by comparing

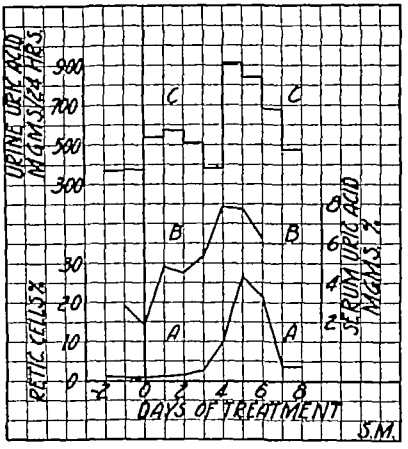

FIG 5 EFFECT OF A MASSIVE DOSE OF LIVER EXTRACT ON THE URIC ACID METABOLISM

Patient S M Before treatment red blood cells 1,120,000 Hemoglobin 29 per cent (Sahli) On 8th day of treatment red blood cells 1,630,000 Hemoglobin 27 per cent (Sahli)

Treatment 30 vials Lilly's liver extract No 343 given at 0 (vertical line) No further medication

A = percentage of reticulocytes

B = concentration of uric acid in the fasting blood serum in milligrams of uric acid per 100 cc.

C = urinary uric acid excretion in milligrams of uric acid per 24 hours

figures 2 and 5 A great rise in uric acid excretion did not follow immediately after the liver extract was given, as would be expected had liver extract been an important source of uric acid precursors

Liver extract which had been subjected to a pressure of 15 pounds

In the first experiment the effect of liver extract on the uric acid metabolism of a normal person using a purine-poor diet was studied After four days of preliminary observation, six vials of liver extract were given daily for ten days, observations being continued for three days after liver extract was discontinued The results are shown in figure 4 No significant changes in the percentage of reticulocytes, in the urinary uric acid excretion or in the concentration of uric acid

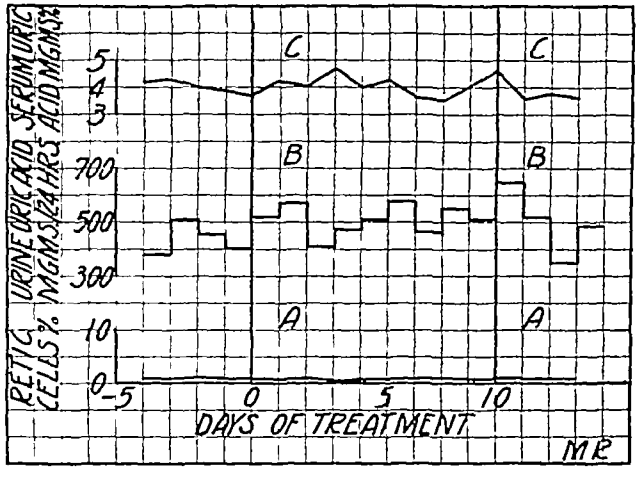

FIG 4 THE EFFECT OF LIVER EXTRACT MEDICATION ON THE URIC ACID METABOLISM IN A NORMAL PERSON

Normal person—M R

Treatment 6 vials Lilly's liver extract No 343 daily from 0–10th day Vertical lines indicate beginning and end of liver extract therapy

A = percentage of reticulocytes

B = urinary uric acid excretion in milligrams of uric acid per 24 hours

C = concentration of uric acid in fasting blood serum in milligrams of uric acid per 100 cc

in the blood serum were observed During the period of liver extract administration, the average daily excretion of uric acid exceeded that of the control periods by 79 milligrams, an amount which probably represents the increase due to the purine materials in liver extract

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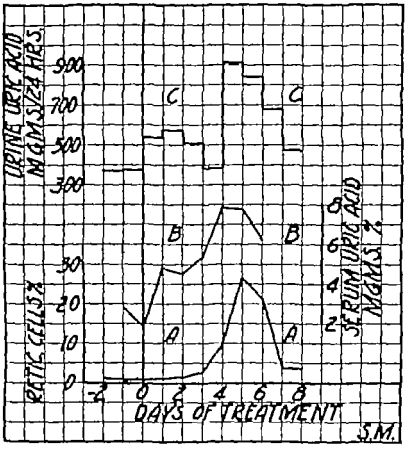

FIG 5 EFFECT OF A MASSIVE DOSE OF LIVER EXTRACT ON THE URIC ACID METABOLISM

Patient S M Before treatment red blood cells 1 120,000 Hemoglobin 29 per cent (Sahli) On 8th day of treatment red blood cells 1,630,000 Hemoglobin 27 per cent (Sahli)

Treatment 30 vials Lilly's liver extract No 343 given at 0 (vertical line) No further medication

A = percentage of reticulocytes

B = concentration of uric acid in the fasting blood serum in milligrams of uric acid per 100 cc

C = urinary uric acid excretion in milligrams of uric acid per 24 hours

figures 2 and 5 A great rise in uric acid excretion did not follow immediately after the liver extract was given, as would be expected had liver extract been an important source of uric acid precursors

Liver extract which had been subjected to a pressure of 15 pounds

and a temperature of 120°F for two hours in an autoclave[4] was given to a patient in daily doses of six vials in a third experiment The

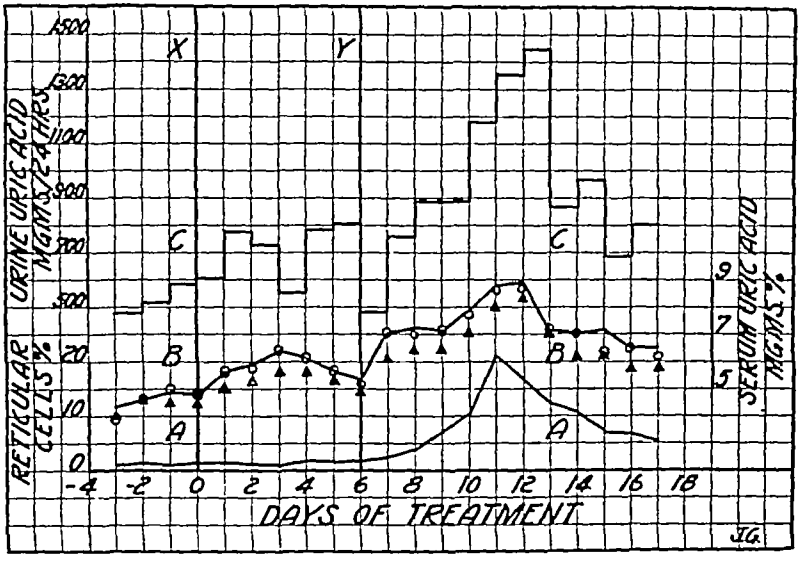

FIG 6 EFFECT OF IMPOTENT (HEATED) AND POTENT LIVER EXTRACT ON THE URIC ACID METABOLISM

Patient J G Before treatment red blood cells 1,250,000 Hemoglobin 32 per cent (Sahli) On 17th day of treatment red blood cells 2,270,000 Hemoglobin 42 per cent (Sahli)

Treatment 6 vials (24 grams) autoclaved Lilly's liver extract No 343, daily 0–6th day Unheated Lilly's liver extract 6 vials daily 6–17th day

A = percentage of reticulocytes

B = concentration of uric acid in fasting blood serum in milligrams of uric acid per 100 cc

Heavy solid line—Folin direct method

Open circles—Folin indirect method (Silver lactate precipitation)

Solid triangles—Morris and MacLeod method (zinc sulphate precipitation)

C = urinary excretion of uric acid in milligrams of uric acid per 24 hours

X = heated liver extract treatment begun

Y = unheated liver extract treatment begun

results are seen in figure 6 The potency of the liver extract had apparently been impaired as a result of heating for there was no

[4] Mentioned through the kindness of Dr Arthur Curtis, whose observations on this method of rendering liver extract ineffective are unpublished

significant increase in the percentage of reticulocytes However a moderate increase in the concentration of uric acid in the blood serum and in the daily urinary excretion of uric acid occurred After six days, potent, unheated liver extract was given in the same dosage of six vials daily Then the usual rise in the percentage of reticulocytes and the usual rapid and great increase of uric acid in the serum and urine took place This experiment indicates that the characteristic

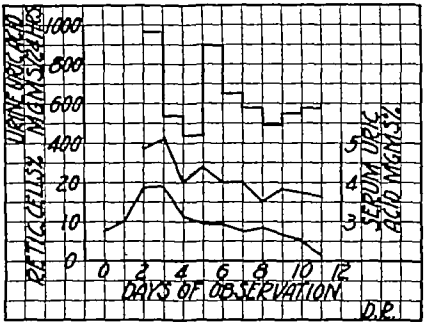

FIG 7 THE URIC ACID METABOLISM DURING SPONTANEOUS REMISSION

Patient D R. On the first day of observation, red blood cells 1,020,000 Hemoglobin 30 per cent (Sahli) On 12th day, red blood cells 1 760,000 Hemoglobin 37 per cent (Sahli)

Treatment None. Spontaneous remission

Lower curve = percentage of reticulocytes.

Middle curve = concentration of uric acid in fasting blood serum in milligrams of uric acid per 100 cc.

Upper curve = urinary uric acid excretion in milligrams of uric acid per 24 hours

changes in the uric acid metabolism which are observed during remission are associated with the remission itself rather than with the feeding of exogenous sources of uric acid in the liver extract Whether the heat to which the liver extract was subjected in this experiment alters the purine constituents of liver extract as well as the substance effective in pernicious anemia is not known While this is considered improbable the existence of such a possibility must be recognized

Added evidence of the endogenous character of the increased uric

acid metabolism during remission was fortunately obtained from a patient undergoing spontaneous remission The increased urinary uric acid excretion and the elevated serum uric acid values, seen in patients in whom remission was induced by liver extract, were observed in this patient whose findings are shown in figure 7 This patient received no liver therapy before or during the period of observation

These experiments furnish evidence of the endogenous character of the increased uric acid metabolism which accompanies remission in pernicious anemia

DISCUSSION

An association between the increased activity of the hematopoietic tissues during early remission and the increased endogenous uric acid metabolism is suggested by the orderly manner in which the uric acid metabolism rises and falls with the rise and fall in the numbers of reticulocytes The sequence of the appearance of increased amounts of uric acid first in the blood and then in the urine and finally of increased numbers of reticulocytes in the blood lends color to the belief that the increased uric acid metabolism is a physiological expression of the rapid maturation of red blood cells, which is an important feature of remission The great numbers of red cell nuclei, lost during the maturation process as red blood cells in the bone marrow assume their non-nucleated form may be an important source of the increased amounts of uric acid found in the blood and urine during early remission Other factors, no doubt, also contribute to the elevated metabolism of purine substances A generalized increase of nuclear metabolism throughout the body during remission seems worth mentioning as another factor possibly of importance

The increase of the concentration of uric acid in the blood serum within 24 hours after the onset of treatment, precedes the reticulocyte increase by one or more days and furnishes the earliest laboratory evidence of oncoming remission

From the experimental evidence, the increased uric acid metabolism appears to be associated with the act of a remission itself, rather than with increase protein consumption, with the manner in which remission is produced or with the presence of materials in liver extract which are theoretically capable of producing uric acid

SUMMARY

1 Before treatment, in patients with pernicious anemia in a complete relapse, using a purine poor diet, the concentration of uric acid in the fasting blood serum varies considerably but usually is normal or less than normal

2 Normal amounts of uric acid are eliminated in the urine before treatment in uncomplicated cases

3 The uric acid metabolism behaves in a very characteristic manner during early remission whether remission is spontaneous or is induced by liver extract There is a prompt increase of the amounts of uric acid excreted, which is, as a rule, apparent within the first 24 hours of treatment

4 During the first two weeks of treatment, the fluctuations of the uric acid metabolism follow those of the numbers of reticulocytes in the blood

5 In the succeeding period, the uric acid metabolism rises to an elevated level which is maintained, within the periods of observation, as long as treatment continues

6 The increased uric acid metabolism during early remission is endogenous in origin and is not accompanied by any outstanding abnormalities in the general nitrogen metabolism

7 The destruction of large numbers of red blood cell nuclei which accompanies the rapid maturation of red blood cells and an increase in general nuclear metabolism throughout the body are advanced as factors which may contribute to the increased uric acid metabolism in pernicious anemia during early remission

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EXPERIMENTS ON THE PATENCY OF THE BLOOD VESSELS OF NEPHRITIC KIDNEYS OBTAINED AT AUTOPSY

By J M HAYMAN, JR

(From the Laboratory of Pharmacology of the University of Pennsylvania, Philadelphia)

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One of the first questions which arise in the study of the physiology of the diseased kidney concerns the capacity of its vessels to permit a normal blood flow If this capacity is normal, alterations in renal function must be attributed either to extrarenal factors, to functional rather than structural changes in renal vessels, or to changes in the renal parenchyma. If conditions in the kidney preclude a normal blood flow, completely normal function is impossible and the basis for interpreting certain types of urinary abnormality has been disclosed The experiments described here were undertaken in the hope of distinguishing those types of kidney disease in which a mechanical, anatomic obstruction to blood flow exists from those in which the structural condition of the vessels may be believed to permit a normal blood flow

Study of changes in the renal vessels in disease by other than histological methods is by no means new Evidence of the capacity of the diseased kidney to transmit blood has been sought in measurements of blood flow after experimental renal injury, in roentgenograms of injected kidneys, and in perfusion of isolated organs The design of the present experiments involved a combination of the last two methods, namely, measurement of the outflow from the renal vein during perfusion under constant conditions, and correlation of this flow with roentgenograms of the vessels after injection, and with histological sections

Direct measurements of renal blood flow in experimental disease have been confined to acute injury Tribe, Hopkins and Barcroft (1) found the renal blood flow measured by Barcroft and Brodie's method, at least as great in a rabbit acutely poisoned by uranium acetate

as in a normal animal In one poisoned by diphtheria toxin, Tribe, Harvey and Barcroft (2) found a decrease in flow, but believed it completely accounted for by the fall in blood pressure Dunn, Dible, Jones and McSwiney (3) detected little change in renal blood flow in acute oxalate nephrosis Schlayer (4) and his pupils showed that the renal vessels of the rabbit gave normal responses to vasoconstrictor and vasodilator substances after injection of chromium salts or corrosive sublimate, while after arsenic or cantharidin the vascular responses were minimal Pearce, Hill and Eisenbrey (5) obtained similar results in dogs The type of renal lesion produced in these experiments is, however, only rarely met in man On the other hand, this type of experiment has the capacity of showing alterations in blood flow resulting from functional as well as structural changes in kidney vessels, which the other types, applicable to human material, have not

Roentgenograms of injected kidneys have been used almost as long as the roentgen ray itself Hauch (6) and Gross (7) showed differences in the vascular architecture of normal and arteriosclerotic kidneys by radiopaque injections which went as far as the interlobular arteries Graham (8), using a suspension of bismuth, succeeded in making complete injections as far as the glomeruli, clusters of which gave an appearance stereoscopically of cone shaped columns around an interlobular artery Acute nephritis, nephrosis, and passive congestion did not produce any detectable alteration from the normal picture Severe arteriosclerosis yielded pictures showing uneven calibre of vessels, wide, club-like interlobar branches, and interlobular arteries which were fewer, shorter and more tortuous The cortex was distinctly narrowed In milder degrees of nephrosclerosis the first changes detectable in the roentgenograms were in the interlobular arteries, which appeared coarser and more tortuous Graham believed he could detect differences in the arterial tree of nephrosclerosis and chronic glomerulonephritis In the latter the cortex was wider, the sclerotic changes milder, the glomeruli few and greatly enlarged

Baehr and Ritter (9), on the other hand, were unable to detect any difference in the vascular tree of primary and secondary contracted kidneys The reproductions accompanying their paper, however, do not permit study of the smaller vessels They believe that extreme

vascular changes develop in patients with chronic diffuse nephritis who survive the glomerulonephritis for a sufficient time, which are pathologically identical with those of primary arterial disease

It has been assumed that in those types of disease giving a normal injection there was no mechanical obstruction to flow in the kidney itself, while in the contracted kidney such an obstruction was present It seems, however, that an artery might offer abnormal resistance to the flow of fluid through it, and still appear normal when injected at high pressure

Perfusion of nephritic kidneys has been practiced since the middle of the last century Dickinson (10) in 1860 perfused human kidneys with warm water at a constant pressure of 8 feet 4 inches of water The average flow in 13 normal kidneys was 11 9 ounces (352 cc.) per minute, while in 6 contracted granular kidneys the average flow was only 2.5 ounces (74 cc.) per minute The perfusability of "large smooth kidneys" was within normal limits The decreased flow he attributed to changes in the minute anatomy, since measurements of normal and nephritic renal arteries and veins failed to show any differences

Thoma (11) carried out similar experiments with solutions of gelatin and of sodium chloride which, together with measurements of the area of renal, interlobular and afferent glomerular arteries, led him to the conclusion that changes in or beyond the glomeruli were responsible for the increased resistance of the contracted kidney to perfusion

Ghoreyeb (12) perfused rabbit kidneys from normal and nephropathic animals with Adler's fluid and with serum He found a decrease in number of drops per minute from the renal vein of animals which had received uranium nitrate, potassium chromate, potassium arsenate, cantharidin, or diphtheria toxin The decrease was proportional to the glomerular change and was maximal twenty-four hours after poisoning He reported that kidneys from animals with spontaneous nephropathies also gave an abnormally low flow He does not give sufficient data to calculate the volume of fluid perfused

Rigo (13) and Doenecke and Rothschild (14) have recently performed similar experiments on human kidneys perfused at very low pressures

All of these investigations have been concerned with the total volume of fluid flowing through the kidney in unit time, and its decrease in the contracted kidney In none have variations in kidney weights been considered, nor comparisons made of the volume of perfusate per unit mass in normal and pathological kidneys, nor of the effects of increase of perfusion pressure on the volume of perfusate Comparisons of the perfusability of a kidney and the appearance of its vessels after injection have not been made

METHODS

Kidneys were removed at the autopsy table and perfused as soon as possible, a few two hours after death, the majority between five and fifteen hours, and a few successfully as late as twenty to twenty-four hours Little difference was detected in the perfusability of kidneys between two and eighteen hours postmortem After twenty-four hours perfusions were usually unsatisfactory, the kidneys were not uniformly blanched and became markedly edematous

In removing the kidneys, renal artery and vein were left as long as possible and care taken not to rupture small vessels around the hilus Kidney and adherent fat were then weighed to the nearest gram At the end of the perfusion the fat was removed and kidney and fat weighed separately There was an error in obtaining the true kidney weight, due to edema developing during perfusion This varied considerably in different kidneys, it was always less, as expected, with acacia than with Ringer's solution When the amount of adherent fat was small, and did not obviously become edematous, its weight was subtracted from the original weight When the amount of adherent fat was larger, covering an appreciable part of the kidney, it also became edematous, due to perfusate leaving the kidney by way of capsular vessels In such cases, after blotting the fat with a towel, fat and kidney were weighed, the assumption made that the degree of edema was the same in both, and the assumed kidney weight was calculated by proportion After weighing, the kidney was put in a dish of water or Ringer's solution at 37°C and cannulae tied in artery and vein

The perfusion fluid, either aerated Ringer s solution or 6 per cent gum acacia in 0 9 per cent saline, was contained in a 4 liter bottle

placed in a water bath at 37°C The outflow tube connected with the arterial cannula was provided with T-tubes for thermometer and manometer and passed under an electromagnet key by which the flow could be automatically interrupted once a second Pressure in the perfusion bottle was maintained by compressed air, and kept constant by a mercury valve which permitted rapid adjustment to the desired pressure The volume of fluid flowing through the kidney was estimated by the outflow from the renal vein The kidney was supported

TABLE 1

Variation in venous outflow with duration of perfusion

Experiment number	Perfusion pressure	Venous outflow
	mm. Hg	*cc per minute*
41	100	208
	150	332
	200	476
	Two liters Ringer's perfused 100 mm. Hg	
	100	196–230
	Two more liters Ringer s perfused 100 mm Hg	
	100	250
	150	370
	200	540
31	100	60
	150	116
	200	184
	100	76
	150	120
	200	160
	100	60

in a metal pan which was arranged to permit collection of all "leak " This leak was made up of fluid escaping from small arterial twigs in the hilus which could not be tied, from the capsular vessels and from the ureter when this was not collected separately The volume of "leak" varied considerably, in many instances only a few cc per minute, in others, as great as the flow from venous cannula The volume of "leak" depended chiefly on the number of vessels perforating the capsule There was no consistent difference in the degree of leak from normal and nephritic kidneys All experiments

Dogs' kidneys perfused with Ringer's solution by the same technique gave flows which were of the same order of magnitude as the blood flow found in the living eviscerated animal by Barcroft and Brodie's method, and showed the same order of increase in flow with increase in perfusion pressure It seems probable that in human kidneys the volume of perfusion fluid is of the same order of magnitude,

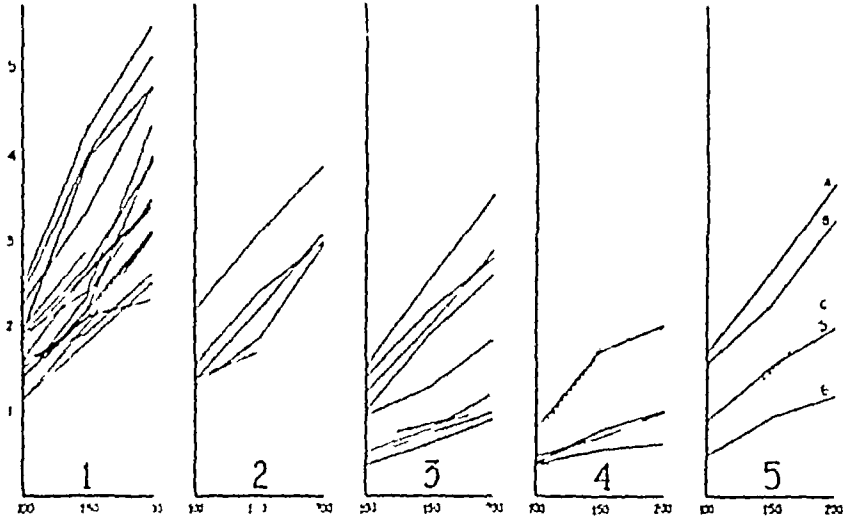

FIG 1 PERFUSION FLOW THROUGH HUMAN KIDNEYS AT DIFFERENT PRESSURES

Abscissae, perfusion pressure in mm Hg, ordinates flow in cc per gram of kidney per minute *1*, normal kidneys, *2* nephroses, *3*, benign arteriolarsclerosis, *4*, acute (----- ---) and chronic (———) glomerular nephritis, *5*, average rates of perfusion flow, (*a*) normal, (*b*) nephroses, (*c*) acute glomerular nephritis, (*d*) arteriolarsclerosis, (*e*) chronic glomerular nephritis

but probably less than the blood flow during life The volumes of acacia perfused were distinctly less than that of Ringer's solution

There was no detectable relation between the volume of perfusate per gram of kidney and age, the vessels of an elderly person which show only the normal amount of change for the age offer no mechanical resistance to the passage of either Ringer's solution or 6 per cent gum acacia solution

Roentgenograms of these kidneys conformed to previous descriptions of the normal arterial tree The primary divisions of the renal artery appeared on the film either just within the kidney shadow or

just outside it. The vessels were slender, gradually decreasing in calibre The branching of interlobar and interlobular arteries were at acute angles The interlobular arteries were slender, parallel and surrounded by columns of glomeruli giving the cortex a delicate, uniformly striated appearance (fig 2)

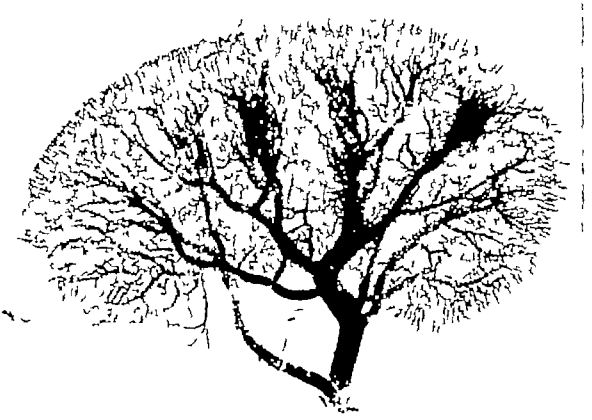

FIG 2 ROENTGENOGRAM OF A NORMAL ARTERIAL TREE (EXPERIMENT 29)

Nephroses

Kidneys showing purely degenerative changes allowed as great perfusion flows as did normal kidneys This group includes a kidney of pregnancy and one of bichloride poisoning The latter is of particular interest The woman had been anuric for four days, had a blood urea nitrogen of 73 mgm per 100 cc , plasma CO_2 content 10 volumes per cent During the 24 hours before death 60 cc. of urine had been obtained by catheter which contained 120 mgm urea nitrogen per 100 cc , or less than twice the blood concentration Grossly the kidney was soft, pale, and the cut edge everted Sections showed morphologically normal glomeruli and extensive necrosis of

the convoluted tubules There was apparently no mechanical interference with the free passage of fluid through the renal vessels It is of course obvious that other factors, especially vascular spasm, may have led to a diminished blood flow during life Experimental evidence however has not established the presence of such a contraction of renal vessels and diminished blood flow produced by poisons whose conspicuous action is on tubule cells Moreover, the conception of a normal blood flow during an anuria from mercury poisoning is in accord with Richards (19) experiments on frogs poisoned by mercury He found a normal glomerular circulation, and that the glomerular filtrate was completely reabsorbed in its passage down the tubule What part blocking of the proximal convoluted tubule with cellular detritus may play in causing anuria in man is unknown Since the edema of the kidney does not interfere with perfusion it throws doubt on the usefulness of decapsulation for mercurial nephrosis with the idea of relieving tension and so increasing blood flow [1] Passive congestion of the kidney did not decrease the volume of perfusate the effect of high venous pressures was not studied Ludwig (20) and Sollmann (15) having shown that this diminishes flow An assumed decrease in renal blood flow in patients with circulatory impairment would seem more properly related to increased pressure in the great veins or to diminished cardiac output rather than to changes produced in the kidney itself by engorgement

No difference in roentgenograms of nephrotic and normal kidneys could be detected

Arteriolarsclerosis

Kidneys from nine cases of benign arteriolarsclerosis have been perfused Two of these (nos 45 and 48) showed only slight thickening of interlobular and afferent arteries in histological section, no 45 appeared entirely normal grossly, while no 48 showed a few depressed arteriosclerotic scars, but no general narrowing of the cortex Both kidneys were from patients who had had hypertension and had died of cerebral hemorrhage Both these kidneys allowed a normal volume of perfusion flow, and did not show any definite abnormality in the

[1] Fischer, however, believes decapsulation effective because of removing a capsular vasoconstrictor reflex Deutsch Med Wchnschr 1926, lii, 992

roentgenograms (fig 3) Four kidneys (nos 1, 18, 25 and 28) presented some narrowing of the cortex and granularity of the surface grossly, and showed histological changes of moderate severity Two of the patients had died from cardiac failure, one of lobar pneumonia, and one of a pulmonary embolus from a thrombosed pelvic vein Only in this patient was any hypertension present during the period of observation No estimations of blood urea nitrogen were available All four had had albuminuria One kidney allowed a perfusion flow per gram within the lower range of the normal group, the other

FIG 3 ROENTGENOGRAM OF THE ARTERIAL TREE OF A KIDNEY SHOWING MILD ARTERIOLARSCLEROSIS HISTOLOGICALLY AND A NORMAL PERFUSION FLOW (EXPERIMENT 45)

three were distinctly below it Roentgenograms showed irregularities and tortuosity of the smaller arteries with a less dense injection of the cortex The remaining three kidneys in this group (nos 31, 33 and 46) showed a very granular surface, marked narrowing of the cortex and advanced arteriolarsclerosis histologically One was from a diabetic, who had had a blood urea nitrogen of 36 mgm per 100 cc , no blood pressure estimation was recorded, one from a person dying from cerebral hemorrhage who had a blood urea nitrogen of 50 mgm per 100 cc , blood pressure 180/130, and one from a senile dement who had 10

mgm. blood urea nitrogen per 100 cc. and blood pressure 165/100. All showed a marked reduction in volume of perfusate per gram of kidney at all pressures. Roentgenograms showed the changes described by H[illegible] Gross and [illegible]. The cortex was narrow, the lumens of the larger vessels uneven in caliber. The interlobular arteries were poorly branched [illegible] single and ended abruptly

Fig. 4. Roentgenogram [illegible] Arteriolosclerotic Kidney [illegible] Injected with [illegible] Gelatin [illegible] (Enlargement × 4[illegible])

instead of tapering gradually. The cortex lacked the striated appearance produced by the rows of glomeruli (fig. 4).

Table 2 shows a comparison of the average volumes of perfusate per gram of kidney per minute in the normal and arteriolarsclerotic kidneys. In the moderately sclerotic group the flow at each pressure is less than in the normal, but at a pressure of 150 mm. Hg the volume is as great as in the normal at 100 mm. In the advanced group the flow at 200 mm. Hg pressure does not equal the normal at half that

pressure That the volume of perfusate through a contracted kidney is less than through a normal one under similar conditions was shown years ago The same relations hold when the flow is expressed per gram of kidney Unfortunately suitable methods are not available for estimating quantitatively the decrease in number of patent glomeruli, so that it is uncertain what parts decrease in number of perfused units and increased resistance in existing vessels play in the diminished volume of perfusate Since the relative increase in volume of perfusate with increase in pressure is of the same order in normal and arteriolarsclerotic kidneys, it seems probable that decrease in the number of patent glomeruli is the more important factor

TABLE 2

Average volume of Ringer's solution per gram of kidney per minute in normal and arteriolarsclerotic kidneys

Perfusion pressure	Normal	Moderate arteriolarsclerosis	Advanced arteriolarsclerosis
mm. Hg			
100	1 7	1 0	0 5
150	2 6	1 8	0 7
200	3 7	2 1	1 0

Nephritis

One example of acute focal glomerulonephritis gave a normal volume of perfusate Two kidneys showing mild acute diffuse nephritis gave perfusion flows below the normal range If this be accepted as evidence of obstruction to blood flow present during life, it lends support to the conception that the mechanism of the oliguria of acute glomerulonephritis and that of mercury poisoning or eclampsia may be essentially different

Kidneys from five cases dying of chronic glomerulonephritis and uremia have been perfused (nos 8, 9, 13, 26 and 34) All the patients had shown low fixed specific gravity of urine, elevation of blood pressure and blood urea nitrogens from 70 to 210 mgm per 100 cc All showed a marked reduction of perfusate at all pressures, both in total volume and in volume per gram of kidney Even at the highest pressure used (200 mm) the flow per gram was less than from the

TABLE 3

Perfusion flows through normal and pathological human kidneys obtained at autopsy

Experiment number	Postmortem	Age	Kidney weight	Perfusion flow, cc. per minute												Histological diagnosis
				Ringer's solution						Acacia						
				Total			Per gram kidney			Total			Per gram kidney			
				Perfusion pressure mm Hg												
				100	150	200	100	150	200	100	150	200	100	150	200	
	hrs	*yrs*	*gm*													
50	17	1	27	56	65	118	2 1	2 4	4 4							Normal
17	24	4	47	64	110	164	1 4	2 3	3 5	62	84	122	1 3	1 8	2 6	
22	7	13	98	240	422	540	2 5	4 3	5 5	192	236	280	1 9	2 4	2 8	
32	19	14	130	200	270	400	1 5	2 1	3 1							
24	14	19	150	208	324	348	1 4	2 2	2 3	116	164	196	0 8	1 1	1 3	
27	23	19	152	200	333	604	1 3	2 2	4 0	124	200	528	0 8	1 3	3 5	
16	6	24	147	240	280	390	1 6	1 9	2 6	206	260	380	1 4	1 8	2 6	
40	9	31	100	224	336	480	2 2	3 4	4 8	220	284	360	2 2	2 8	3 6	
11	22	37	134	262	388		2 0	2 9								
41	9	38	152	208	332	476	1 4	2 2	3 1	120	128	144	0 8	0 8	1 0	
29	18	40	153	178	280	372	1 2	1 8	2 4							
42	9	45	156	260	404	540	1 7	2 6	3 5							
35	12	52	122	141	246	378	1 2	2 0	3 1	92	128	200	0 8	1 1	1 6	
47	7	53	165	246	320	472	1 5	1 9	2 9	280	344	440	1 7	2 1	2 7	
49	17	63	160	380	620	824	2 4	3 9	5 2							
21	17	66	128	243	506	618	1 9	4 0	4 8	240	310	470	1 9	2 4	3 7	
43	11	68	101	192	270	400	1 9	2 7	4 0	68	80	100	0 7	0 8	1 0	
36	11	69	129	224	336	444	1 7	2 6	3 4	144	164	216	1 1	1 3	1 7	
5	10	19	150	210	260		1 4	1 7								Simple nephrosis
7	15	25	101							118			1 2			Simple nephrosis
14	5	44	137	306	424	540	2 2	3 1	3 9							Cholemic nephrosis
15	8	26	171	265	412	520	1 6	2 4	3 0							HgCl nephrosis
37	6	34	175	240	400	544	1 4	2 3	3 1							Pregnancy nephrosis
39	19	45	172	224	320	510	1 3	1 9	3 0	200	248	312	1 2	1 4	1 8	Simple nephrosis
45	5	39	137	208	352	488	1 5	2 6	3 6	134	200	268	1 0	1 5	2 0	Mild arteriolarsclerosis
48	6	72	140	172	280	408	1 2	2 0	2 9	158	180	336	1 1	1 3	2 4	
1	2	48	170	124		160	0 7		0 9							Moderate arteriolar-sclerosis
18	20	67	100	143	229	284	1 4	2 3	2 8	124	198	248	1 2	2 0	2 5	
25	22	60	136	142	260	356	1 0	1 9	2 6	180	224	300	1 3	1 6	2 2	
28	11	47	171	162	220	316	0 9	1 3	1 9	124	156	288	0 7	0 9	1 7	
31	8	77	153	76	120	184	0 5	0 8	1 2	50	80	116	0 3	0 5	0 7	Advanced arteriolar-sclerosis
33	7	47	101	36	62	90	0 4	0 6	0 9							
46	20	72	75	33	54	74	0 4	0 7	1 0							

TABLE 3—*Concluded*

Experiment number	Postmortem	Age	Kidney weight	Perfusion flow cc. per minute												Histological diagnosis
				Ringer's solution						Acacia						
				Total			Per gram kidney			Total			Per gram kidney			
				Perfusion pressure, mm. Hg												
				100	150	200	100	150	200	100	150	200	100	150	200	
	hrs	*yrs*	*gm.*													
19	8	23	198	150	241	412	0 8	1 2	2 1							Acute glomerulonephritis
20	10	60	160	128	277	384	0 8	1 7	2 4							
8	12	52	215	86			0 4				20			0 1		Chronic glomerulonephritis
9	10	36	74	30	41	47	0 4	0 6	0 6	9	20	20	0 1	0 3	0 3	
13	24	25	80	65	137	163	0 8	1 7	2 0							
26	9	24	95	38	74	98	0 4	0 8	1 0	9	17	23	0 1	0 2	0 2	
34	8	35	155	75	100	160	0 5	0 6	1 0	24	44	44	0 2	0 3	0 3	
23	5	38	218	278	484	711	1 3	2 2	3 3	190	248	307	0 9	1 1	1 4	Acute focal glomerulonephritis

normal group at 100 mm The average flow per minute was 0 5 cc at 100 mm perfusion pressure, 0 9 cc at 150 mm , and 1 2 at 200 mm These averages are very close to those found in advanced arteriolarsclerosis

Whether the ultimate pathological process is the same in the two groups, as maintained by Baehr and Ritter (9), or whether there are subtle differences, these data do not indicate There was no significant difference in kidney weights in the two groups The patients in the sclerotic group had shown only moderate evidence of renal insufficiency and did not die in uremia, while the patients in the nephritic group had all shown severe renal insufficiency and had died in uremia The roentgenograms of the nephritic kidneys resembled the arteriolarsclerotic in general appearance, but showed some points of difference The irregularity and tortuosity of the arteries was less marked, the cortex was not narrowed to the same degree, but the cortical injection was even more scanty than in the arteriolarsclerotic group (fig 5) If the actual number of patent glomeruli were known, the analysis might be carried further

Hypertrophy of remaining glomeruli is more evident in nephritic than in arteriolarsclerotic kidneys A given volume of fluid may, in the nephritic kidney, traverse a greatly reduced number of glomeruli, many of which are enlarged, while in the arteriolarsclerotic kidney the same volume passes through a greater number of glomeruli of more nearly normal size The filtering surface in the latter would be greater, and the volume of filtrate per unit volume of blood greater at the same pressure Kidneys from patients dying in uremia and showing purely arteriolarsclerotic changes have not been obtained

FIG 5 ROENTGENOGRAM OF THE ARTERIAL TREE OF A CHRONIC GLOMERULAR NEPHRITIC KIDNEY WHICH GAVE THE SAME VOLUMES OF PERFUSATE PER GRAM AS THE KIDNEY IN FIGURE 4 (EXPERIMENT 34)

SUMMARY

Forty-two normal and nephritic human kidneys have been perfused with Ringer's solution or acacia at different pressures to distinguish in which structural interference to flow existed The results have been compared with roentgenograms of the vascular tree after injection of bismuth and with histological sections

1 There was no decrease in volume of perfusate per gram of kidney with advancing years

2 Kidneys showing only degenerative changes showed no evidence of mechanical obstruction in the blood vessels They permitted as great a perfusion flow as did normal kidneys No abnormality was detected in roentgenograms of the vascular tree after injection

3 Kidneys presenting benign arteriolarsclerosis showed a definite decrease in volume of perfusate per gram at a given pressure, proportional to the degree of histological change When the degree of sclerosis was moderate, the volume of perfusate per gram at 150 mm Hg perfusion pressure equalled the normal at 100 mm pressure In kidneys showing advanced lesions the volume flow per gram at 200 mm pressure was less than the normal at 100 mm Roentgenograms showed irregular, tortuous arteries, and a narrow cortex with fewer interlobular arteries

4 Acute diffuse glomerulonephritis showed a diminished volume of perfusate at each pressure

5 Chronic diffuse glomerulonephritis showed a marked reduction of perfusion flow per gram of the same magnitude as advanced arteriolarsclerosis Roentgenograms resembled the picture of arteriolarsclerosis, but the cortex was less narrowed while the number of injected interlobular arteries and glomeruli were less

The histological diagnosis of many of these sections has been confirmed by Dr Baldwin Lucke, to whom I express my thanks I am also indebted to Dr Eugene Pendergrass and to Dr I S Ravdin for making the roentgenograms

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GLUCOSE EXCRETION IN BRIGHT'S DISEASE[1]

By JAMES A HAWKINS, EATON M MacKAY AND DONALD D VAN SLYKE.
(From the Hospital of the Rockefeller Institute for Medical Research, New York)

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The occurrence of hyperglycemia and glycosuria in nephritis has been observed and studied by Neubauer in 1910 and a number of subsequent investigators A review of this subect has been included in the article on carbohydrate metabolism in nephritis by Linder, Hiller and Van Slyke (1925) They found that hyperglycemia and glycosuria were most frequent in cases with marked deficit of renal function, that nephritics with fasting hyperglycemia when fed glucose showed abnormally high and prolonged blood sugar curves, similar to those in mild diabetes, that nevertheless the respiratory quotients after glucose feeding rose as in normal subjects, indicating a normal combustion of glucose The abnormality appeared to lie in a retarded transfer of glucose from blood to tissues, rather than in a retarded combustion The renal threshold of sugar excretion appeared to be low in some cases, as evidenced by the appearance of a positive qualitative Benedict test for reducing substances in the urine

However, as shown by Eagle (1926–27) and by Van Slyke and Hawkins (1929), normal urine may contain substances equivalent in reducing power to 0 1 per cent or more of glucose, but only about one-tenth of the reduction is actually due to sugar capable of fermentation, like glucose To obtain interpretable data concerning the permeability of nephritic kidneys to glucose it is therefore necessary to base conclusions upon determinations of the fermentable sugar in the urine The present studies are based on such determinations

[1] A preliminary report of results was presented by the authors at the 1928 meeting of the American Society of Biological Chemists (Hawkins, MacKay, and Van Slyke, 1928)

METHODS

The blood sugar determinations were made by the microgasometric ferricyanide method of Van Slyke and Hawkins (1928) on cutaneous blood obtained by a clean deep prick with a sharp needle The blood obtained in this way is practically arterial (Lundsgaard and Moller, 1922) We did not determine the fermentable blood sugar, but used "total blood sugar" values, because the non-fermentable material determined in blood by the ferricyanide method has been shown to be a relatively small and constant value (Van Slyke and Hawkins, 1929)

The reducing substances of the urine, fermentable and non-fermentable, were determined quantitatively by the Van Slyke-Hawkins gasometric methods (1928, 1929) In considering urinary excretions our conclusions have been based entirely on fermentable sugar values, since the unidentified non-fermentable reducing material in urine is relatively so much that in normal subjects it constitutes nearly all of the total reducing material

Glucose ingestion tests The subjects of these studies were given no food or fluids for a 12-hour period preceding the determinations Each subject was given 200 cc of water at 7 00 a m Blood was taken at 7 00 and 8 00 a m , and urine collected for the period from 7 00 to 8 00 a m Glucose was given in 200 cc of water at room temperature at 8 00 a m All intervals indicated on the charts are measured from this point Blood specimens were taken at 0 25, 0 5, 0 75, 1 0, 1 25, 1 75, 2 15, 2 75, 3 15 and 3 75 hours The urine specimens were collected at 0 5, 1 0, 1 5, 2 0, 2 5, 3 0, and 4 0 hours The subject remained in bed throughout the test and received no other fluid, food, or medication during this period The amount of glucose given was 1 gram for each kilo of ideal weight estimated for the subject's height, age and sex, by figure 1 of McIntosh, Moller, and Van Slyke (1928) The glucose used was Merck's "C P "

RESULTS

Blood sugar curves, and curves indicating the amounts of fermentable and non-fermentable reducing substances in the urine were obtained on 3 normal persons and on 19 patients with nephritis

The blood and urine curves of the normal subjects are given in figure 1 Figures 2 to 11 show the curves obtained in the different forms and stages of nephritis

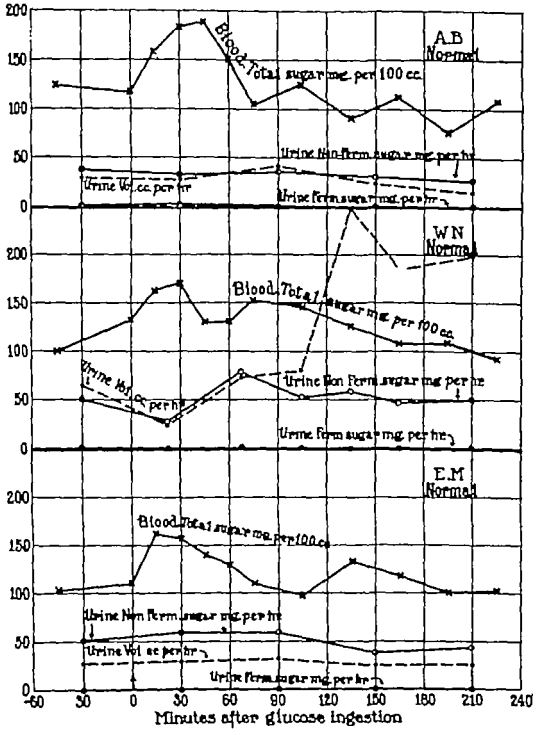

FIG 1 DATA ON NORMAL SUBJECTS

In table 1 is given a summary of the tests made on patients with Bright's disease The Addis classification (1925) for Bright's disease is used, and the patients are grouped according to the divisions and subdivisions of this classification The age, sex, blood pressure and

relative extent of edema at the time of the test are reported in Table 1 in order to give some aid in judging the patient's clinical status The 2-hour phthalein excretion and the urea excreting ability in terms of the blood urea clearance (cc of blood cleared of urea by 1 minute's excretion determined as described by Moller, McIntosh, and Van Slyke, 1928) are noted to indicate the state of renal function at the time of the tests The clearance values are given in per cent of average

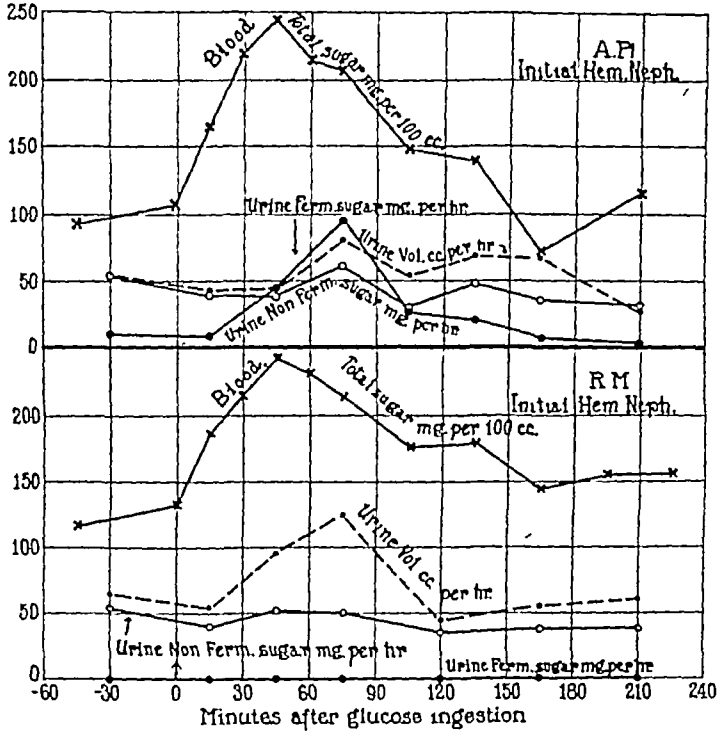

FIG 2 DATA ON SUBJECTS WITH INITIAL HEMORRHAGIC NEPHRITIS

normal, viz , 54 cc of blood per minute for the "standard clearance," estimated for urine output of 1 cc per minute, 75 cc per minute for "maximum clearance" with urine volumes exceeding 2 cc per minute

DISCUSSION

In normal subjects our data, taken with those of Eagle (1926–27) indicate that excretion of fermentable sugar is usually less than 5 mgm

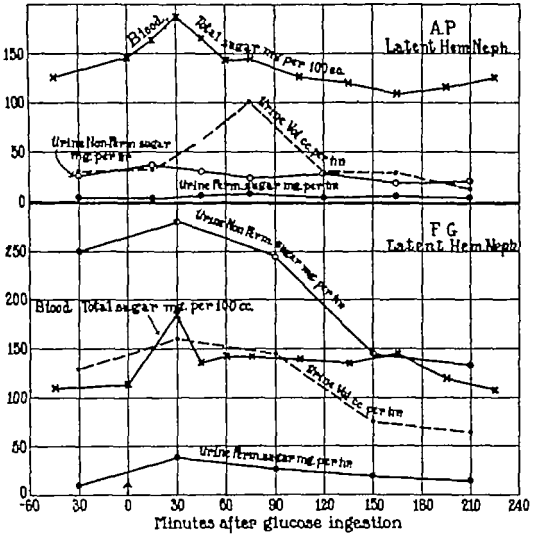

FIG 3 DATA ON SUBJECTS WITH LATENT HEMORRHAGIC NEPHRITIS

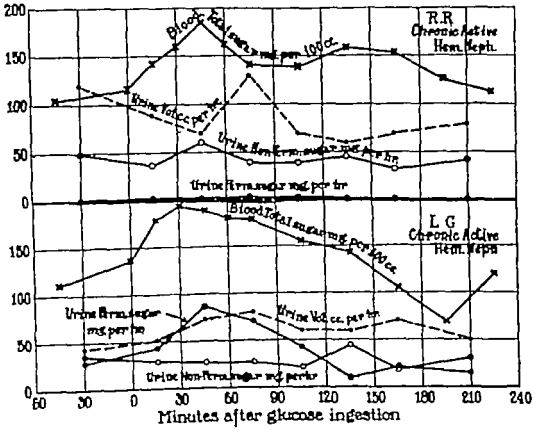

FIG 4 DATA ON SUBJECTS WITH CHRONIC ACTIVE HEMORRHAGIC NEPHRITIS

per hour during fast, and is not increased above this level after consumption by mouth of 1 gram of glucose per kilo body weight It is known, of course, that there are otherwise normal subjects who have

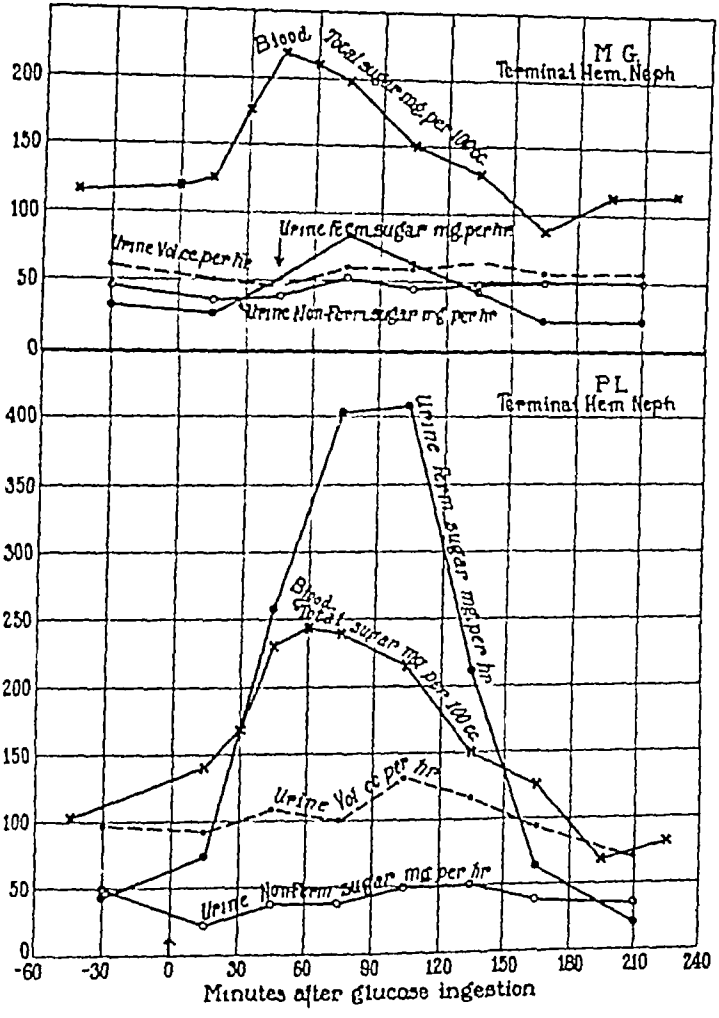

FIG 5 DATA ON SUBJECTS WITH TERMINAL HEMORRHAGIC NEPHRITIS

continual or intermittent glycosuria, which appears attributable to a low renal threshold for glucose, since the glycosuria occurs in the presence of normal blood sugar values Such cases appear, however, to be relatively rare Our controls and those of Eagle may be taken

to represent the usual normal behavior, marked departure from which, if frequent in any given condition, may be considered as evidence of deviation from the probable normal behavior of the subjects examined

Abnormal glycosurias (compared with the above controls) were shown by all our cases with degenerative Bright's disease (nephrosis)

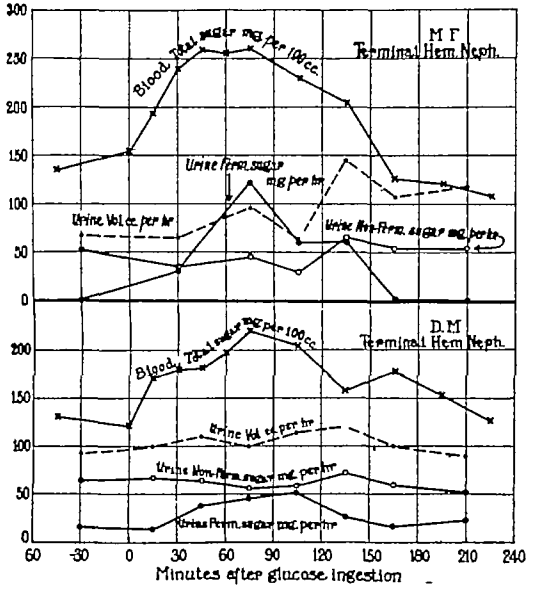

FIG 6 DATA ON SUBJECTS WITH TERMINAL HEMORRHAGIC NEPHRITIS

and by all in the terminal stage of hemorrhagic nephritis In excretion of fermentable sugar after glucose feeding all these patients exceeded the normal controls, and in excretion during fasting all except one, a terminal hemorrhagic, exceeded the controls

The most marked glycosurias occurred in the degenerative group 3 out of 6 cases showed over 0 3 per cent of fermentable sugar in the urine during fast, and over 1 per cent after glucose feeding

In cases of initial and moderately advanced hemorrhagic nephritis, about half showed relative glycosuria, both fasting and after glucose ingestion

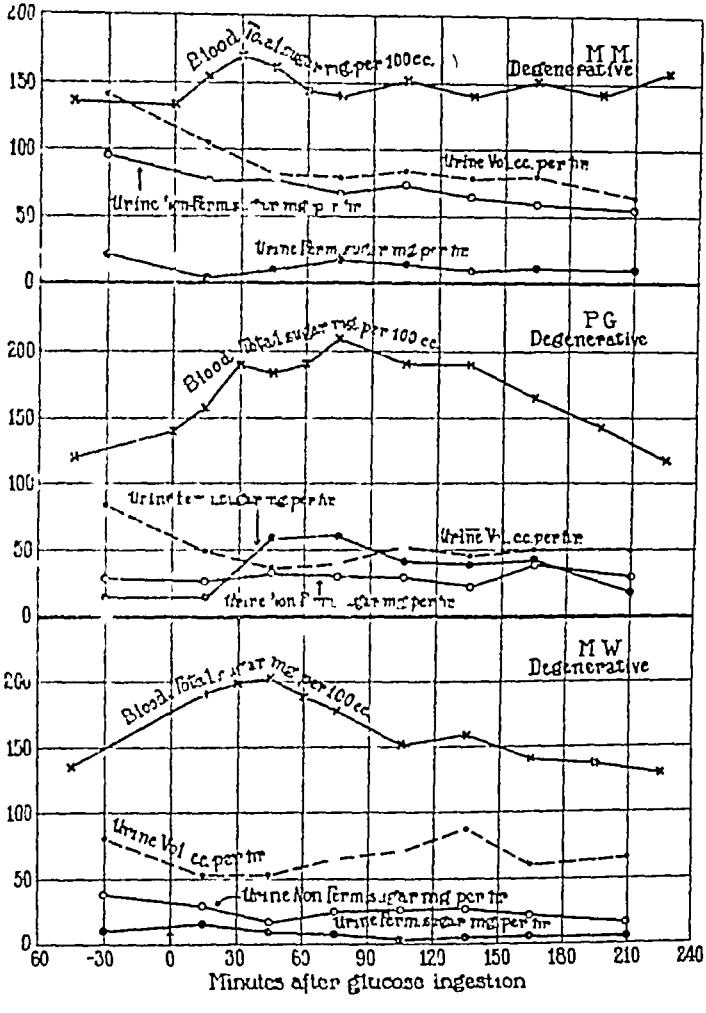

FIG 7 DATA ON SUBJECTS WITH DEGENERATIVE HEMORRHAGIC NEPHRITIS

Of the 3 arteriosclerotic cases one showed a definite glycosuria (50 mgm per hour) after glucose feeding, none while fasting

Comparison of blood sugar curves with fermentable sugar excretion indicates that the glycosurias in all types of the disease appear attribut-

able to low excretion thresholds rather than to high blood sugar values In some cases, it is true, particularly in the terminal hemorrhagic group, the blood sugar peak after glucose ingestion is so high (210–266 mgm per cent) that glycosuria would be expected over a normal threshold However, nearly all such cases showed glycosuria also in the fasting state, with relatively low blood sugar values The work of Linder, Hiller, and Van Slyke (1925) has shown that somewhat high

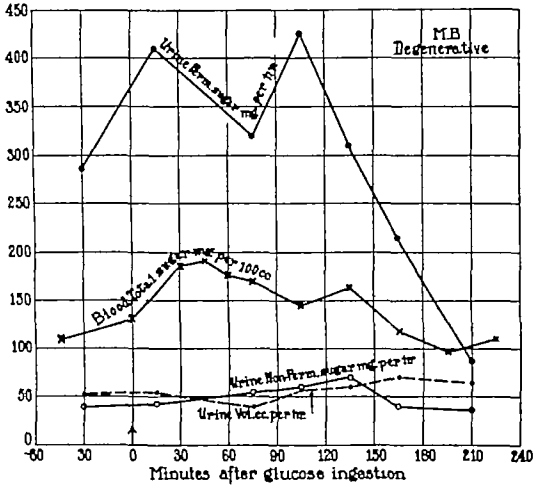

FIG 8 DATA ON A SUBJECT WITH DEGENERATIVE HEMORRHAGIC NEPHRITIS

and prolonged blood sugar curves after glucose feeding are common in nephritis, and are unconnected with any retardation in the rate at which glucose can be burned, or with any other evidence of diabetes

In the degenerative cases showing gross glycosuria, both fasting and after glucose feeding, the blood sugar curves were within normal limits

It appears probable that many cases heretofore reported as combined nephritis and diabetes have been nephritis with renal glycosuria

It is possible that the glycosuria is due to failure of the renal tubules to reabsorb glucose from the glomerular filtrate Such an hypothesis

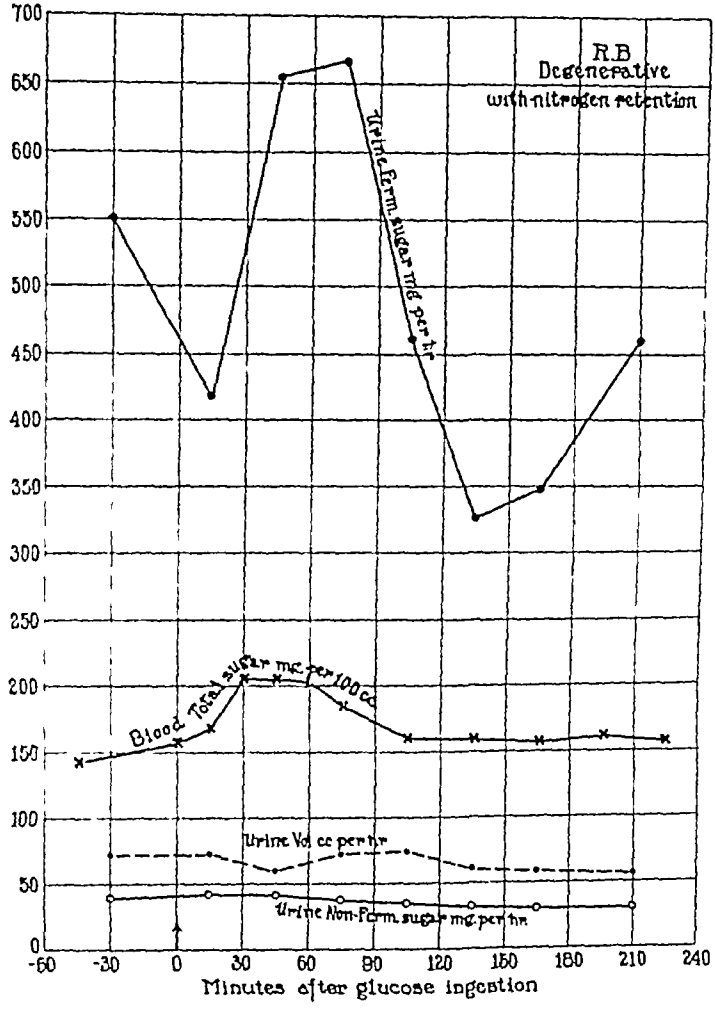

FIG 9 DATA ON A SUBJECT, R B , WITH DEGENERATIVE HEMORRHAGIC NEPHRITIS WITH NITROGEN RETENTION

appears somewhat plausible because of the especially marked glycosurias observed in certain of the degenerative cases, in which the tubules are known to be especially involved

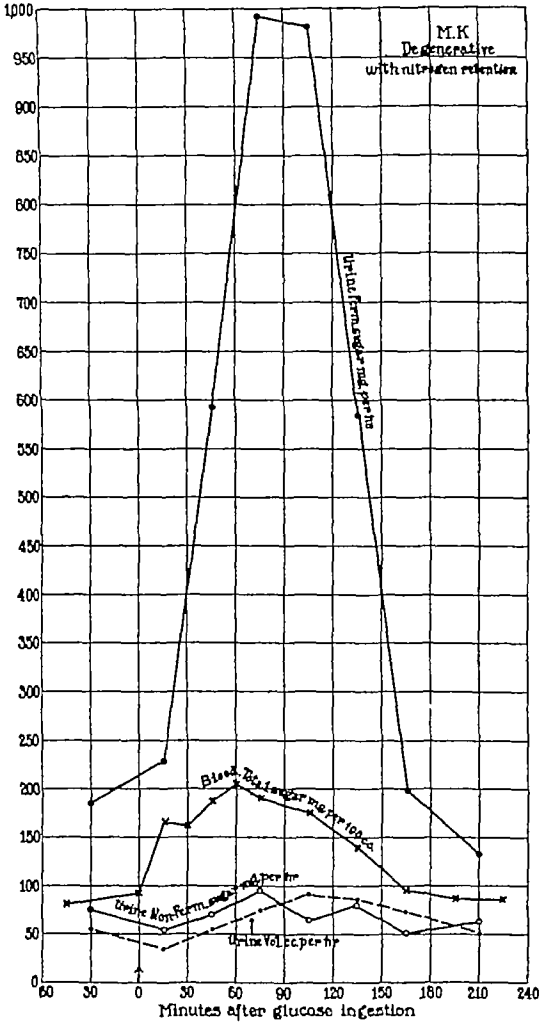

FIG 10 DATA ON A SUBJECT, M K., WITH DEGENERTIVE HEMORRHAGIC NEPHRITIS WITH NITROGEN RETENTION

Case number	Hospital number	Diagnosis: Bright's disease: Type	Diagnosis: Bright's disease: Stage	Complications	Age	Sex	Heart size	Blood pressure	Eye grounds	Edema	
					yrs						
R M	6353	Hemorrhagic	Initial		38	F	Normal	138/90	Normal	0	1
A Pl	6139	Hemorrhagic	Initial		19	M	Normal	150/95	Normal	0	2
A P	6251	Hemorrhagic	Latent		13	M	Increased	110/60	Normal	+	
F G	6162	Hemorrhagic	Latent		20	F	Slightly increased	200/115	Normal	0	1
L G	6123	Hemorrhagic	Active		19	F	Normal	150/105	Hemorrhages	+	3
R R	6475	Hemorrhagic	Active		25	F	Normal	165/114	Normal	++	8
M G	5074	Hemorrhagic	Terminal		15	M	Normal	150/90		0	45
P L	5210	Hemorrhagic	Terminal	Chronic middle ear	30	M	Slightly increased	150/90		0	78
D M	6238	Hemorrhagic	Terminal		16	M	Increased	135/85	Normal	0	46
M F	6183	Hemorrhagic	Terminal		30	F	Increased	220/150	Hemorrhages retinitis	0	68
P G	6482	Degenerative	Active		25	M	Normal	105/75	Normal	+++	8
M M	6184	Degenerative	Active		18	M	Normal	105/75	Normal	+++	6
M B	6172	Degenerative	Active	Pulmonary tuberculosis	29	M	Normal	110/70	Normal	+	12
M W	6473	Degenerative	Active		12	M	Normal	115/70	Normal	+++	18
R B	5505	Degenerative	Terminal		11	M	Normal	115/60	Normal	++	22
M K	5949	Degenerative	Terminal	Empyema	20	M	Normal	130/80	Normal	+++	37
K C	6102	Arterio-sclerotic			51	F	Slightly increased	150/85	Normal	0	15
M Fe	6446	Arterio-sclerotic			49	F	Normal	235/155	Normal	0	11
M Go	6466	Arterio-sclerotic		Cardiac failure	49	F	Greatly increased	240/145	Retinitis	+	31

on patients

Urine (excretion per 12 hours)																Renal function		Sugar in blood and urine			
ma proteins					Protein	Formed elements										Phthalein excretion (2 hours)	Standard blood urea clearance	Fasting blood sugar	Fasting fermentable urine sugar	Maximum blood sugar after glucose ingestion	Maximum fermentable sugar in urine after glucose ingestion
						Erythrocytes	Leucocytes and epithelial cells	Casts													
	Globulin	Total	A/G ratio					Total	Hyaline	Blood	Fatty	Epithelial	Granular	Waxy	Failure						
per cent	*per cent*	*per cent*			*gm.*	*millions*	*millions*	*millions*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent of injected*	*per cent of average normal*	*mg. per cent*	*mg. per hour*	*mg. per cent*	*mg. per hour*
3 15	7 61	1 41		0 9	106 00	50 88	0 58	100	0	0	0	0	0	0		60 9	48 3	117	0 0	243	2 0
2 54	6 86	1 70		1 6	13 49	11 48	1 08	83	3	0	0	14	0	0		37 0	33.5	94	12 0	245	97 0
4 26	5 78	0 36		3 1	7 27	4 10	0 26	100	0	0	0	0	0	0		83 2	74 7	125	5 0	187	8 0
2 08	5 14	1 47		2 5	11 02	3 39	1 75	100	0	0	0	0	0	0		54 8	35 2	109	22 0	184	50 0
2 60	4 89	0 88		5 4	9 20	27 00	13 95	16	0	0	28	64	0	0		19 8	19 8	109	31 0	192	86 0
2 68	3 91	0 46		2 9	25 46	26 80	12 46	90	0	8	0	2	0	0		56 4	46 3	104	0 0	186	8 0
2 26	5 94	1 63		3 3	39 44	23 20	4 06	0	0	0	0	0	0	100		13 6	15 9	115	32 0	218	89 0
2 03	5 34	1 63		3 6	36 48	5 93	0 52	0	0	0	0	0	0	100		4 9	13 5	102	46 0	243	410 0
2 54	5 61	1 21		4 6	190 68	77 20	4 48	67	13	0	0	12	0	8		14 1	18 7	131	18 0	221	52 0
2 44	6 13	1 50		1 9	++	+	+	0	0	0	0	0	0	100		8 0	6 3	135	4 7	261	122 0
3 35	4 06	0 21		5 4	0 24	12 40	4 96	33	0	25	0	34	8	0		56 7	58 3	121	14 0	210	62 0
3 47	4 81	0 39		6 5	0 31	6 82	1 86	70	0	20	10	0	0	0		67 8	144 0	134	25 0	169	20 0
2 72	4 64	0 70		7 5	0 33	24 48	5 30	80	0	16	4	0	0	0		54 6	55 9	111	287 0	188	410 0
2 32	3 97	0 71		3 8	0 06	14 11	0 88	65	0	35	0	0	0	0		50 1	43 8	135	12 0	202	16 0
3 12	4 41	0 41		3 9	0 40	4 29	1 48	30	0	0	0	43	0	27		10 2	22 2	143	550 0	205	628 0
2 90	4 86	0 68		3 7	0 39	38 53	57	10	0	10	10	25	5	40		7 0	18 6	80	189 0	204	1 095 0
3 05	7 37	1 42		0 1	0.58	0 43	0 14	100	0	0	0	0	0	0		50 0	78 2	117	1 0	157	1 0
2 81	7 2	1 59		0 3	0 58	0 32	0 32	100	0	0	0	0	0	0		74 0	88 5	112	0 0	191	52 0
2 79	6 00	1 15		0 8	3 04	0 23	0 08	50	0	0	0	50	0	0		28 9	11 1	118	9 0	201	12 0

STUDIES OF THE CIRCULATION IN THREE CASES OF MORBUS CAERULEUS

BY LUCIEN D LUTREBANDE, W R MARSHALL AND J C. MEAKINS

(From the University Clinic Department of Medicine McGill University and Royal Victoria Hospital, Montreal)

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INTRODUCTION

Studies on the anatomical peculiarities of congenital cardiac disease, with explanations of their embryonic development, have been comparatively common Attention has been focused upon the numerous deviations from the normal which may occur as a developmental anomaly, but comparatively few studies have been made upon the functional disturbance of the circulation Further, little or no attention has been paid to those means of physiological compensation and adaptation which would necessarily have to occur in order to maintain life There has been the well known differentiation into two broad classes,—the cyanotic and non cyanotic groups The circulatory problems underlying the latter are but little different from those which occur in acquired cardiac disease On the other hand, in *Morbus Caeruleus* (the cyanotic type of a case) a number of questions of great physiological importance arise The present communication deals with three such cases all of which have been studied in more or less complete detail

MATERIAL

Case no 1 W R. Came under observation at the age of twelve years giving a history of having suffered from shortness of breath weakness, and blueness of the hands and face since infancy On attempting exercise he could walk only a few feet before the cyanosis became intense, and persistence in the effort produced unconsciousness

On physical examination he was a poorly developed thin male child, with pronounced cyanosis of the hands, ears, and mucous membranes. There was pronounced clubbing of the fingers and toes. The chest was prominent and rachitic, the venules of the upper thorax were quite distinct The cardiac apex beat was

palpable in the fifth left interspace just beyond the nipple line On percussion the cardiac dullness was 3 cm to the right and 10 to the left of the mid-sternal line On auscultation the sounds were loud, the first sound at the apex was re-duplicated

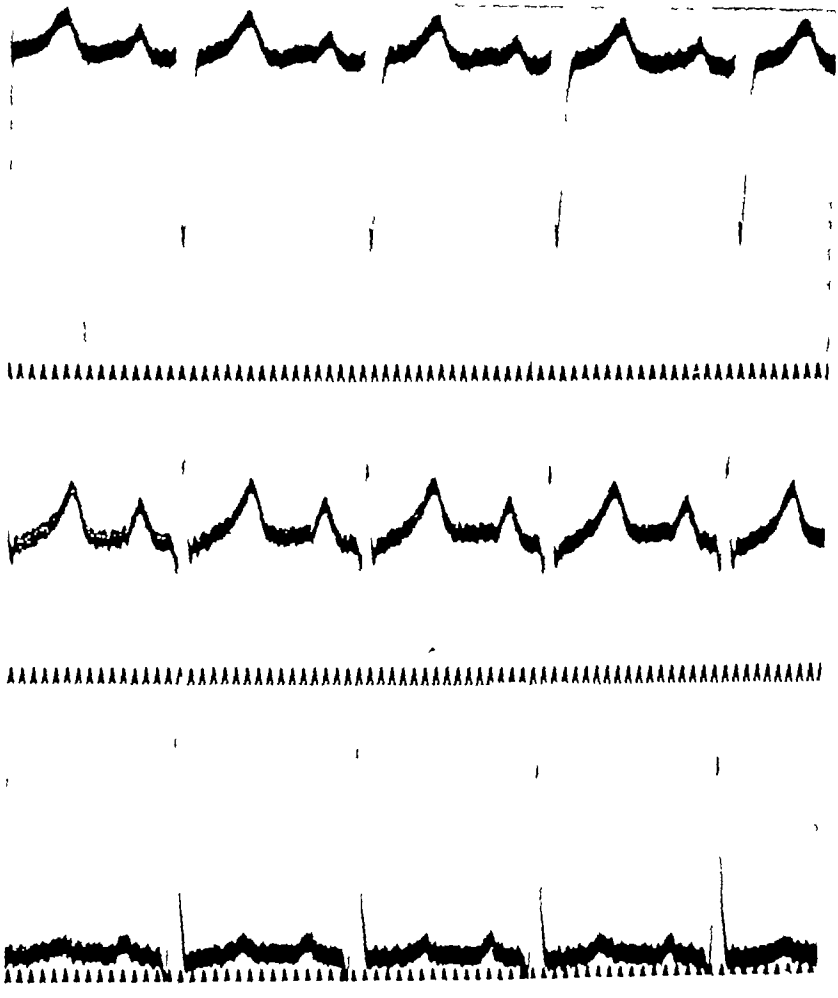

Fig 1 Regular Rhythm A-V Conduction Normal Right-sided Preponderance of Concenital Type and High Voltage Intra-ventricular and Intra-Auricular Conduction Time Normal

1 cm = 1 mv

but there were no murmurs audible The pulse rate was 118, and the systolic blood pressure was 138 mm An electrocardiograph showed a right-sided preponderance (fig 1) Examination of the blood showed the erythrocytes to num-

ber 8,500,000 haemoglobin 175 per cent The ratio between the plasma and corpuscles was found by the haematocrit to be corpuscles 68 5 per cent, plasma 30 5 per cent.

He died suddenly on November 11, 1922 The post mortem revealed the following findings The whole body and particularly the hands and face were deeply cyanosed On incision the blood was dark and almost too viscid to flow The lungs showed a small amount of oedema and emphysema The liver was enlarged, congested and fatty, while the spleen measured 12½ x 7½ x 5 cm , was firm and had the appearance of chronic congestion The mesenteric glands were enlarged The heart was enlarged in all directions, especially the right auricle and ventricle There was a fibrous cord representing the ductus arteriosus The right auricle was distended and on opening it there was present a well marked Eustachian valve and a slit like and definitely patent foramen ovale The wall of the right ventricle was extremely hypertrophied, being twice as thick as that of the left The intraventricular septum was deficient and a glass rod could readily be passed from the right ventricle into the aorta while a glass rod of finer calibre could be passed into the pulmonary artery The mitral orifice was normal but the left ventricle was dilated and there was the aforementioned communication with the right ventricle

Summary Pulmonary stenosis, deficient intraventricular septum, hypertrophy of the right ventricle patent foramen ovale, and passive congestion of the viscera

Case no 2, M M Aged 13 Weight 29 kilos Height 137 cm The patient complained that she had had breathlessness, weakness, and blueness of the skin since infancy On examination she was found to be under-developed, very cyanosed with pronounced reticular mottling of the skin The fingers were long and tapering but there was comparatively little clubbing of the tips

The physical examination was normal except for the circulatory system The apex beat was in the fifth space, 10 cm from the mid sternal line It was not pronounced on inspection but gave a thudding impression to the palpating finger There was a palpable systolic thrill in the fourth left space about 7½ cm from the mid line. The cardiac dullness measured 3 cm to the right and 11 to the left of the mid sternal line The heart sounds were well heard and were accompanied by a harsh systolic murmur heard over all areas but most pronounced in the third left intercostal space about 4 cm from the mid line. The second sound of the mitral area was of a slapping character and occasional extrasystoles were detected The pulse was 115 per minute, easily compressible, with occasional irregularity of the rhythm On immersing the hand and forearm in hot water the cyanosis practically disappeared On slight exertion it became intense and although the patient could walk about at a slow pace she had a much greater limit of exertion than case 1, but she could not walk upstairs. The electrocardiograph showed pronounced right sided preponderance (fig 2) The examination of the blood showed

7,250,000 red cells, and haemoglobin 145 per cent The haemotocrit readings showed the corpuscles to occupy 55 per cent by volume and the plasma 45 per cent

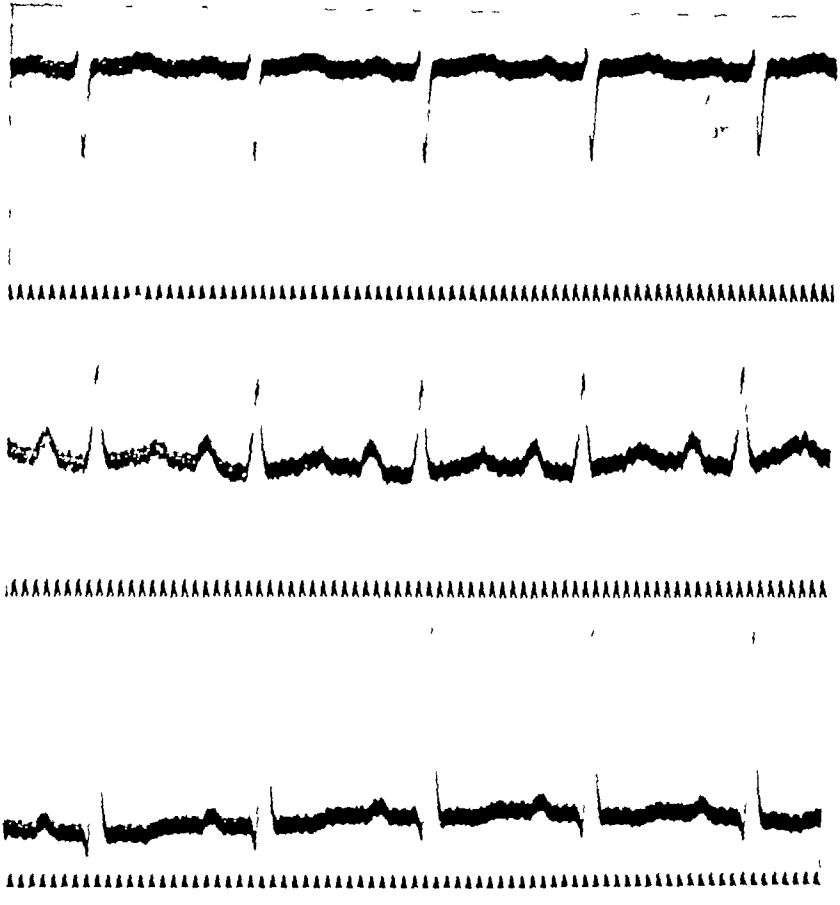

FIG 2 REGULAR RHYTHM A-V CONDUCTION TIME NORMAL RIGHT-SIDED PREPONDERANCE OF CONGENITAL TYPE WITH HIGH VOLTAGE INTRA-VENTRICULAR AND INTRA-AURICULAR CONDUCTION TIME NORMAL

"T" wave in Lead III is diphasic, and somewhat flattened in Leads I and II

On the 20th of March, 1928, she was in good physical condition, aged 19 years, apart from breathlessness and cyanosis on exertion

Case no 3, F A Came under observation at the age of nineteen with a history of cyanosis and dyspnoea on exertion since childhood and following slight exertion

he was usually troubled with a cough, although he was able to do some light work One of his chief complaints was frequent throbbing headaches

On physical examination there was generalized cyanosis particularly of the face and hands, and pronounced clubbing of the finger tips. Examination of the

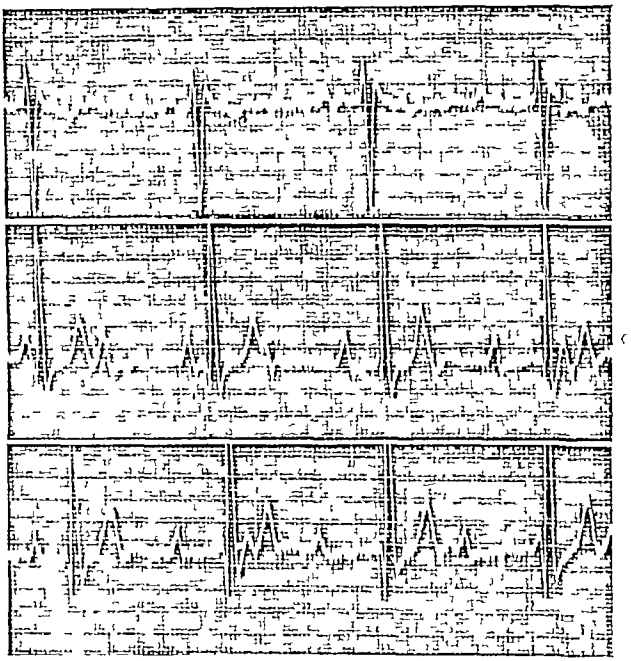

FIG 3 COMPLETE HEART BLOCK. RIGHT SIDED PREPONDERANCE OF CONGENITAL TYPE AND HIGH VOLTAGE. INVERSION OF 'T' WAVE IN LEAD I

Ventricular rate—45 Auricular rate —90 1 m.v = 3 c.m

thorax showed good development with bulging of the praecordium breathing was rapid, being 40 per minute The lungs were normal The cardiac apex beat was in the fifth left interspace 7¼ cm from the mid sternal line. The cardiac dullness was 8 cm to the left and 3 cm. to the right of the mid-sternal line No thrills were palpable and no murmurs were audible on auscultation The pulse

was 40 per minute, and synchronous with respiration The systolic blood pressure was 126 mm and the diastolic 73 mm The arterial walls were not palpable The pulsation could be felt in the finger tips The electrocardiograph showed a right-sided preponderance (*fig 3*) and a complete heart block Examination of the blood showed erythrocytes to be 8,000,000 and haemoglobin 161 per cent The haematocrit readings were corpuscles 63 per cent and plasma 37 per cent An x-ray of the chest revealed the heart to be rounder than usual and the aorta to be small

TABLE 1

Data on cases 1, 2 and 3

	Case 1	Case 2	Case 3
Arterial blood O saturation, *per cent*	63 4*	70*	81
Arterial blood CO_2 content, *volumes per cent*	28*	33 6*	34 3
Venous blood O_2 saturation, *per cent*	16 5	21	25 2
O Capacity of blood, *volumes per cent*	32 29	27 24	29 8
Haemoglobin, *per cent*	174	147	161
Alveolar air			
CO , *mm*	23	25 3	27
O , *mm*	114	116	117 5
Expired air, *liters per minute*	5 03	5 26	12 82
CO_2, *per cent*	2 12	2 07	2 05
O_2, *per cent*	18 53	17 72	18 7
CO_2 given up per minute, *cc*	96 1	139	234 6
O_2 taken up per minute, *cc*	114 5	178	312 8
Respiratory quotient	0 84	0 78	0 75
Venous CO fully oxygenated, *mm*	33	33 4	
Pulmonary blood flow determined by the ethyl iodide method, *liters per minute*			3 51
Pulmonary blood flow determined by the CO method, *liters per minute*	1 75	2 78	
Pulse rate	108	100	40

* The exact accuracy of these findings is open to doubt on account of the great difficulty in obtaining even small amounts of arterial blood

RESPIRATORY FUNCTION

The respiratory rate and rhythm in cases 1 and 2 were within normal limits In case 3, however, over a long period of observation it has been found that the respiratory rate synchronizes with that of the heart rate An adequate explanation of this phenomenon has not been discoverable This rapid respiratory rate is reflected in the large minute volume of expired air in this case It amounted to 12 82

liters per minute The details of the respiratory and blood gas data are set forth in table 1

CARBON DIOXIDE DISSOCIATION CURVES

The carbon dioxide dissociation curves in all cases showed a pronounced lowering as seen in figures 4, 5, and 6 On plotting the partial

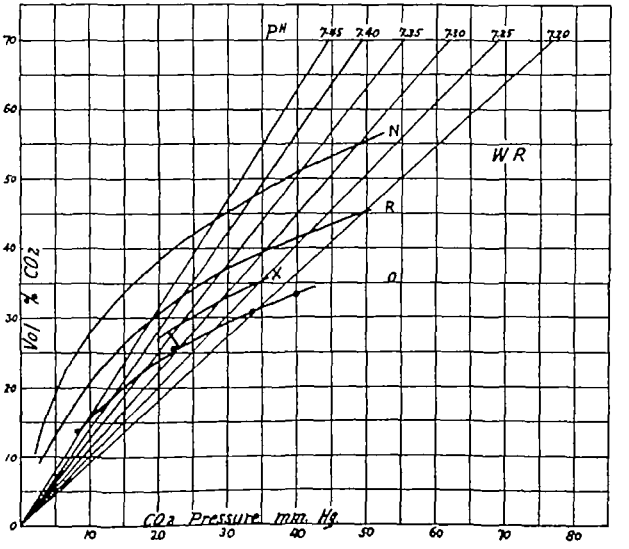

FIG 4 CARBON DIOXIDE DISSOCIATION CURVES OF CASE 1

N—normal fully oxygenated CO_2 curve, *R*—fully reduced CO_2 curve, *O*—fully oxygenated CO_2 curve *X*—CO_2 curve at an oxygen saturation as found in the arterial blood

pressure of CO_2 of the alveolar air on the curve of the fully oxygenated blood (as it might be presumed to be as it left the lungs) it is found that the CO_2 content of such blood was 25 5 cc volumes per cent in case 1, 30 5 cc volumes per cent in case 2, and 33 5 cc volumes per cent in case 3 But the CO_2 content of the radial blood was definitely greater in each case as follows

Case	CO_2 content, cc volumes per cent in pulmonary blood	CO_2 content, cc. volumes per cent in radial blood
1	25 5	28 0
2	30 5	33 6
3	33 5	34 3

The elevation of the dissociation curve however produces a lowering of partial pressure of the CO_2 in arterial blood although the content is increased

Case	Partial pressure of CO_2 in the pulmonary blood	Partial pressure of CO_2 in the radial blood
	mm Hg	*mm Hg*
1	23	21
2	25 3	23 5
3	27	26

If a similar comparison be made of the pH of the pulmonary and radial it will be found that there is a distinct shift towards alkalinity in the latter

CO_2	pH of the pulmonary blood	pH of the radial blood
1	7 30	7 37
2	7 36	7 40
3	7 35	7 37

The sum total of these findings would indicate that there had been an efficient attempt to compensate for the disturbed aeration of the arterial blood

THE OXY-HAEMOGLOBIN DISSOCIATION CURVES

The oxy-haemoglobin dissociation curves (figs 7, 8 and 9) show in all cases a distinct shift to the left, as would be expected if an alkalosis were present These curves are similar to those found by the Royal Society Expedition to the Andes (1) and conform to the oxy-haemoglobin curves which Barcroft (2) found to occur when the haemoglobin was concentrated in human blood It may also be noted that the CO_2 curves are of a similar character to those found by this Expe-

dition When the findings of the blood gases in the arterial blood of those suffering from mountain sickness and these cases of congenital heart disease are compared, the similarity is most striking In the cases here reported the oxygen saturation of the arterial blood was 63 4

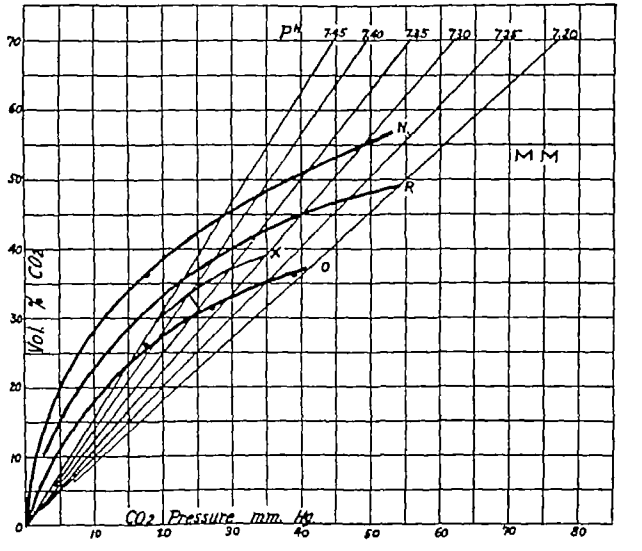

FIG 5 CARBON DIOXIDE DISSOCIATION CURVES OF CASE 2

N—normal oxygenated CO_2 curve, *R*—fully reduced CO_2 curve, *O*—fully oxygenated CO_2 curve, *X*—CO_2 curve at an oxygen saturation as found in the arterial blood.

per cent in case 1, 70 per cent in case 2, and 81 per cent in case 3, while the CO_2 content was respectively 28 cc., 33 6 cc. and 34 3 cc., volumes per cent In these cases the degree of oxygen de-saturation of the arterial blood was greater than that found in any people living at high altitudes

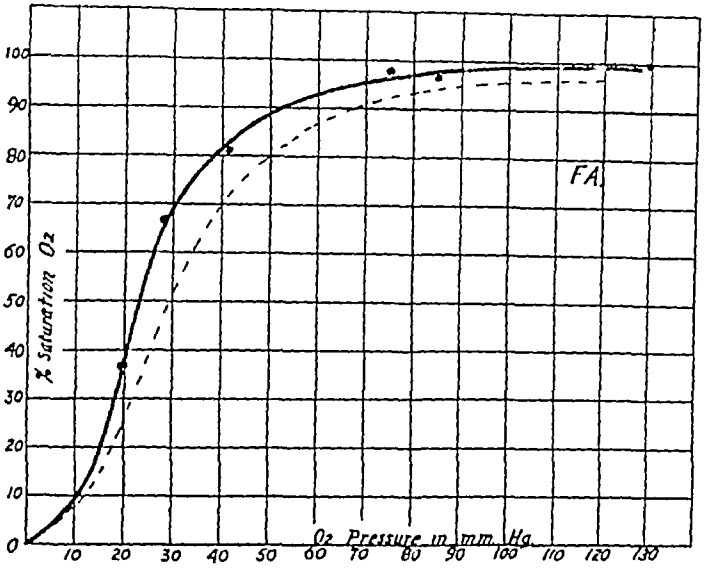

FIG 9 OXY-HAEMOGLOBIN DISSOCIATION CURVE OF CASE 3

Solid line that of patient, dotted line that of normal

TABLE 2

Venous shunt in case 3 using the method of Weiss and Lowbeer

O_2 capacity of blood from radial artery = 29 8 cc. volumes per cent.
O_2 content of pulmonary blood leaving lungs = 29 8 × 95 5 = 28 45 cc. volumes per cent
O_2 consumption per minute (B M R) = 234 6 cc
Lung flow determined by ethyl iodid method = 3 51 liters per minute

$$O_2 \text{ intake by lungs} = \frac{234\ 6}{3\ 51} = 66\ 8 \text{ cc per liter of blood}$$

O_2 content of blood in radial artery = 24 3 cc volumes per cent
O_2 content of mixed venous blood = 28 45 − 6 68 = 21 77 cc volumes per cent.
Let X = the venous shunt in liters
Total blood flow = 3 51 + λ liters
(A) Total O_2 in mixed arterial blood = (3 51 + λ) 24 3 × 10
(B) Total O_2 in circulation = (3 51 × 28 45 + 21 77λ) 10

$$A = B$$
$$(3\ 51 + \lambda)\ 24\ 3 \times 10 = (3\ 51 \times 28\ 45 + 21\ 77X)\ 10$$
$$25\ 3X = 147$$
$$X = 5\ 82 \text{ liters per minute}$$
$$5\ 82 + 3\ 51 = 9\ 33 \text{ liters total flow per minute}$$
$$(5\ 82 - 9\ 33)\ 100 = 62\ 4 \text{ per cent venous shunt}$$

TABLE 3

Venous shunt in case 3 calculated by using Lundsgaard's figure for oxygen consumption in the tissues (5 volumes per cent)

O_2 capacity in radial artery = 29 8 cc. volumes per cent
O_2 content in pulmonary vein blood = 29 8 × 95 5 per cent = 28 45 cc. volumes per cent
O_2 content in radial artery = 24 3 cc volumes per cent
O_2 in venous blood = 24 3 − 5 = 19 3 cc. volumes per cent
Let λ = the venous shunt in percentage of the total blood flow,
$100 - \lambda$ = the percentage amount of blood entering the arterial system from the pulmonary veins

$$O_2 \text{ in radial artery blood (volumes per cent)} = \frac{\text{Venous } O_2 \ \lambda}{100} + \frac{O_2 \text{ in pulmonary veins}}{100} (100 - \lambda)$$

$$24\ 3 = \frac{19.3\lambda}{100} + \frac{28\ 45\ (100 - \lambda)}{100}$$

$$2430 = 19\ 3X + 2845 - 28\ 45\lambda$$

$$\lambda = 45\ 4 \text{ per cent venous shunt}$$

TABLE 4

Venous shunt in case 3 calculated by using the oxygen content of blood of the arm vein as representing that in the right auricle

O_2 capacity in radial artery = 29 8 cc. volumes per cent
O_2 content in pulmonary vein blood = 29 8 × 95 5 per cent = 28 45 cc. volumes per cent
O_2 content in radial artery = 24,3 cc. volumes per cent
O_2 content in arm vein = 7 5 cc. volumes per cent
Let λ = the venous shunt in percentage of the whole blood flow,

$$O_2 \text{ in radial artery (cc. volumes per cent)} = \frac{\text{Venous } O_2 \times \lambda}{100} + \frac{O_2 \text{ in pulmonary veins}}{100} (100 - \lambda)$$

$$24\ 3 = \frac{7\ 5\lambda}{100} + \frac{29\ 45\ (100 - \lambda)}{100}$$

$$2430 = 7\ 5\lambda + 2845 - 28\ 45\lambda$$

$$20\ 9\lambda = 415$$

$$\lambda = 19\ 85 \text{ per cent venous shunt}$$

TABLE 5

Comparison of three methods of calculating venous shunt

Case	Venous shunt calculated by the Weiss Lowbeer method	Venous shunt calculated by subtracting 5 cc. volumes per cent of oxygen from the radial blood O_2 content for the venous blood	Venous shunt calculated by using the O_2 content of the arm vein blood as representing the general venous blood
	per cent shunt	*per cent shunt*	*per cent shunt*
1	Negative	68 8	40 5
2	Negative	58	34
3	62 4	45 4	19 8

SECONDARY ALTERATIONS IN TOTAL SERUM CALCIUM AFTER THE ADMINISTRATION OF GLUCOSE AND INSULIN

By READ ELLSWORTH

(From the Medical Clinic of the Johns Hopkins Hospital Baltimore)

(Received for publication July 1, 1929)

In studying the metabolism of a case of idiopathic hypoparathyroidism, in which the mechanism of the action of parathormone[1] was under observation Albright and Ellsworth (1) found that the

ERRATA

VOL. VIII, NO 1, DECEMBER, 1929, PP 114–120

Article by Hawkins, MacKay, and Van Slyke, "Glucose Excretion in Bright's Disease"

Figures 7, 8, 9, 10 and 11 The word "hemorrhagic" should be deleted from the legends of these figures

Figure 10 "degenertive" should be "degenerative"

far as to suggest that the primary effect might be on the phosphorus metabolism

We have watched for some time to see if following the administration of parathormone there was, in the blood determinations, any lag of either Ca or P behind the other, but both in the case of hypoparathyroidism (1) and in normal individuals (unpublished) the first sample of blood to show a change in P concentration also showed a change in total Ca Even at hourly intervals the changes appeared to be synchronous

[1] Preparation introduced by Collip and prepared by Eli Lilly and Company

It therefore seemed wise to study the behavior of the total blood Ca when the phosphorus was suddenly lowered by some other well-known mechanism

Some years ago Harrop and Benedict (4) demonstrated that the administration of glucose or glucose and insulin brought about a fall

TABLE 1

Blood sugar and chloride and serum calcium and inorganic phosphorus in patients 1 to 6

(Milligrams per 100 cc)

Patient	Constituent	Fasting	1 hour	2 hours	4 hours
1	Sugar	91	114	97	100
	P	4 9	3 9	4 2	5 4
	Ca	10 7	11 3	11 8	10 6
2	Sugar	80	113	111	90
	P	3 9	3 0	3 2	4 5
	Ca	11 2	10 85	12 3	10 9
3	Sugar	82	140	80	80
	P	4 5	3 7	3 2	4 2
	Ca	9 0	9 6	9 8	9 8
	Cl	482	497	474	489
4	Sugar	91	178	86	98
	P	4 3	3 8	3 8	4 4
	Ca	8 9	8 75	9 25	9 05
	Cl	472	446	478	456
5	Sugar	86	51	70	62
	P	5 6	4 9	4 0	5 2
	Ca	9 5	10 25	10 2	10 6
6	Sugar	100	125	60	40
	P	4 2	3 5	2 4	3 8
	Ca	9 85	10 1	10 45	9 8
	Cl	467	476	503	433

of blood phosphorus Since that time it has been shown that the decrease in blood phosphorus is due in all probability to the formation of hexose-phosphate It was decided therefore to use glucose and insulin as the means of producing a sudden lowering of blood phosphorus

Accordingly six individuals were chosen who were, as far as could be determined, free from any disorder of calcium, phosphorus or glucose metabolism Each patient after 14 hours fasting was given by mouth 50 grams of glucose in coffee and 50 units of insulin Blood was taken just before the administration of insulin and at one, two and four hours thereafter The blood specimens were allowed to stand 20 to 30 minutes to ensure thorough clotting, then centrifuged and the

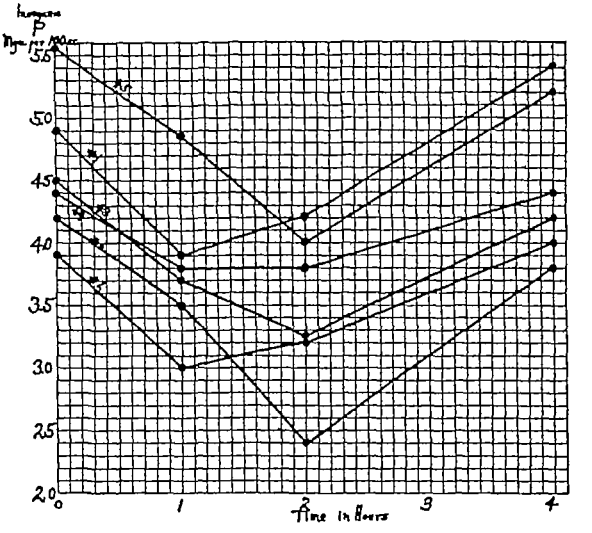

CHART 1 COMPOSITE SERUM INORGANIC PHOSPHORUS CURVES

Numbers over the curves indicate case numbers. Milligrams per 100 cc.

serum pipetted off The determinations were started at once The sugar estimations were made on whole blood, the phosphorus and total calcium on serum, the phosphorus was estimated by the method of Benedict and Theis (5) the calcium by the Fiske method described by Blackfan and Hamilton (6)

The alterations in the calcium and phosphorus are shown in table 1 and charts 1 to 3

OBSERVATIONS

It will be seen, that in all cases the phosphorus was lowered at the end of one hour, remained low at the end of two hours, but usually had returned at the end of four hours toward the fasting level The calcium was in four instances raised at the end of one hour and in all six raised at the end of two hours At the end of four hours the

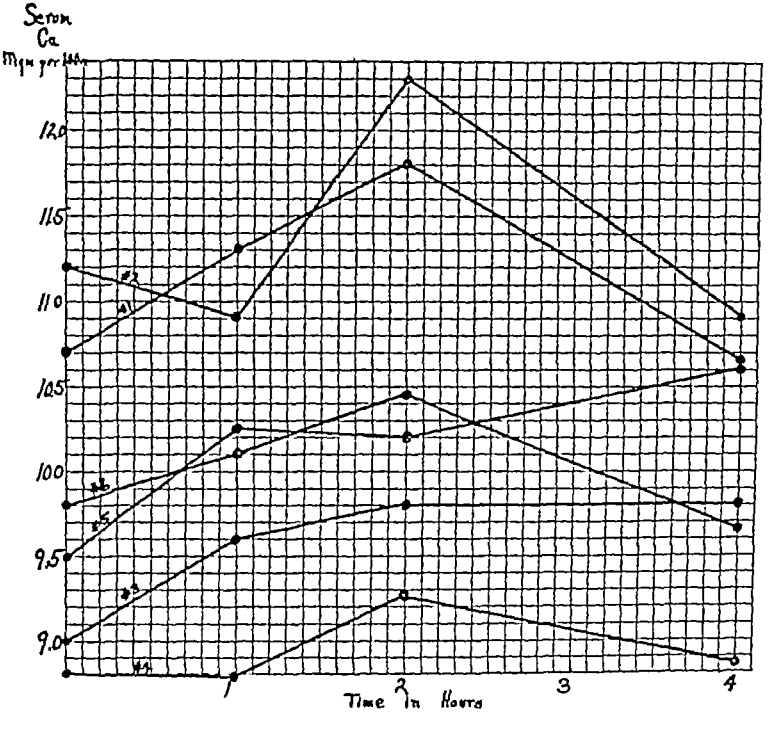

CHART 2 COMPOSITE SERUM CALCIUM CURVES

Numbers over the curves indicate case numbers Milligrams per 100 cc

calcium in four of the six cases had fallen toward the control fasting level, in one instance, it was constant, in one it had risen still further

Two other patients, one (1A), a mild diabetic in the metabolism ward, the other (2A), suffering from general paresis, were studied in a slightly different manner They received 25 units of insulin before their usual breakfast, which included in both cases fruit, toast and eggs and in addition 25 grams of glucose The determinations were

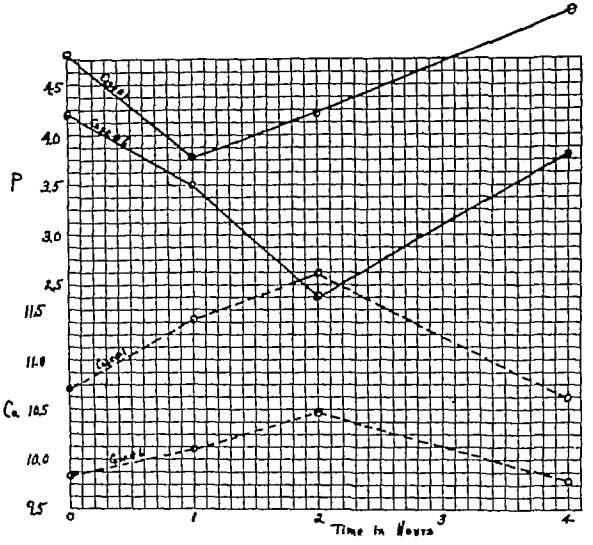

CHART 3 SAMPLE CASES SERUM CALCIUM AND INORGANIC PHOSPHORUS CURVES
Milligrams per 100 cc

TABLE 2

Blood sugar and serum calcium and inorganic phosphorus in patients 1A and 2A

(Milligrams per 100 cc.)

Patient	Constituent	Fasting	1 hour	2 hours	3 hours	5 hours
1A	Sugar	142	138′	137	100	62
	P	6 6	5 5	5 3	5 1	5 1
	Ca	10 3	10 9	10 8	10 3	9 8
Refractive Index		1 3500	1 3508	1 3498	1 3498	1 3495
2A	Sugar	104	115	73	70	
	P	4 1	3 6	3 6	3 5	3 7
	Ca	9 7	10 1	9 9	10 6	11 0

carried out in the same manner as in the other six patients except that the blood specimens were obtained fasting and at one, two, three and five hours after breakfast The results are shown in table 2 and chart 4 *In both of these cases there was a fall of phosphorus and a rise of calcium* In case 2A the rise of calcium was out of proportion to the fall of phosphorus This may have been due in part to absorption of calcium received in the food To remove this possibility the other six individuals received only glucose

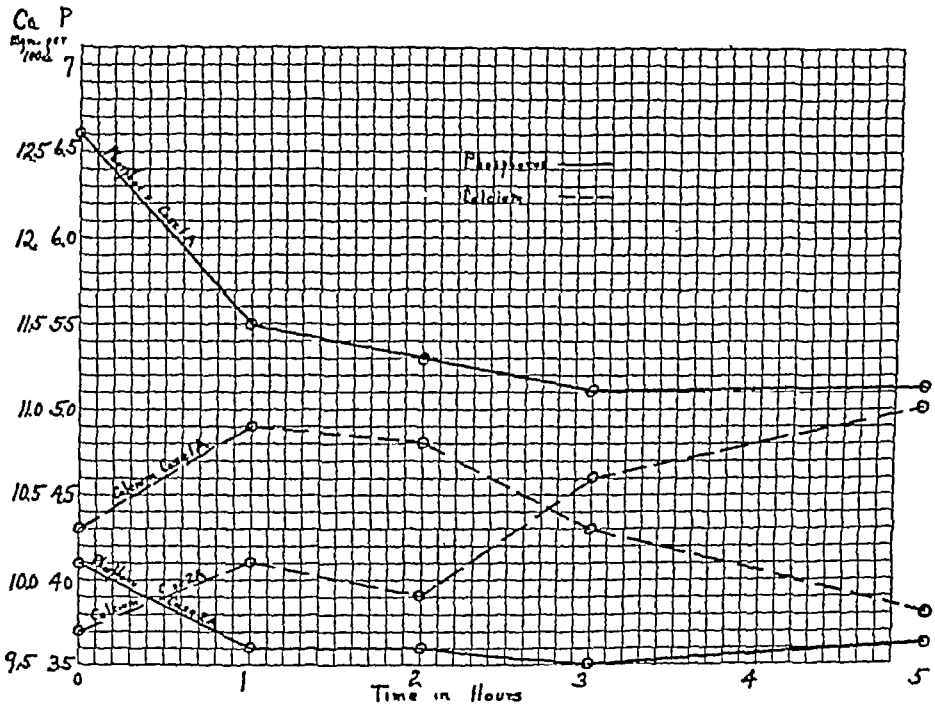

CHART 4 FIVE-HOUR SERUM CALCIUM AND INORGANIC PHOSPHORUS CURVES
Milligrams per 100 cc

DISCUSSION

Observations upon eight individuals indicate that, when the blood phosphorus is lowered by the administration of glucose and insulin the total blood calcium rises The increase in serum calcium under these circumstances has not, so far as I am aware, been observed previously It does not seem probable that the increase in total blood calcium

could be due to an anhydremia and decrease in blood volume, such as has been described by Drabkin and Edwards (7) and Drabkin and Shelkret (8) after the injection of insulin in animals, for the anhydraemia observed by them occurred only in association with hypoglycaemia, whereas it will be seen (tables 1 and 2) that, inasmuch as the patients in the present series received glucose as well as insulin, the rising calcium concentrations occurred in most instances during periods when the blood sugar was also increasing The values of the blood chlorides (table 1) and of the refractive indices in case 1A (table 2) add still further evidence to show that there was not sufficient change in blood volume to account for the rise in the blood calcium

It has previously been pointed out in some observations made upon the relative concentrations of blood calcium and blood phosphorus that the demonstrable rise in total blood calcium occurs almost synchronously with the demonstrable fall in blood phosphorus, and the present experiments show again the difficulties that are encountered when one attempts to determine by blood analyses which of these elements is the first to change It is fairly well established, however, that one effect of the injection of glucose and insulin is the formation of hexose phosphate and on this account it appears highly probable that in this series of observations the primary action of the insulin was upon the blood phosphate and that the rise in blood calcium occurred in all likelihood as a secondary phenomenon

The explanation of the observed rise may be that, as the phosphorus is lowered in the serum saturated with $Ca_3(PO_4)_2$, more calcium and phosphate are mobilized from the bones so that the product of Ca ions times PO_4 ions tends to be kept constant As would be expected, if this were the explanation, it is seen that, in general, (table 1) the greater the fall of blood phosphorus, the greater the rise in blood calcium Had we a satisfactory method for the determination, it would be interesting to know whether there was any alteration in the ratio of ionized and unionized calcium during the rise in total calcium

The rapidity of the response of blood phosphorus and calcium to the administration of glucose and insulin suggests that tetanic seizures, associated with high blood phosphorus and low blood calcium, such as one encounters in parathyroid tetany, may be relieved by glucose

and insulin Moreover, it is possible that glucose and insulin may enhance the action of parathormone Studies to determine these points are in progress

CONCLUSIONS

1 The administration of glucose and insulin to six normal individuals, one diabetic patient and one patient with general paresis resulted in a prompt fall of phosphorus as shown formerly by Benedict and Harrop

2 There was a definite tendency for the total serum calcium to rise

3 The first rise in calcium was usually observed in the same hour as the first fall in phosphorus—the changes gave the appearance of being synchronous

4 Both the phosphorus and calcium effects were seen to have disappeared usually at the end of four hours

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THE DETERMINATION OF THE TOTAL HEAT ELIMINATED BY THE HUMAN BEING[1]

By MARGARET WOODWELL JOHNSTON and L H NEWBURGH

(From the Department of Internal Medicine Medical School University of Michigan, Ann Arbor)

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It is desirable to be able to determine accurately the total energy exchange of human subjects who are to be observed for a number of consecutive days during which a variety of diets may be fed and a certain amount of activity must be permitted The chamber calorimeter is in general impractical, nor is the average heat production obtained through repeated determination by means of indirect calorimetry satisfactory We have accordingly taken up the question whether a third method recently brought forward by Benedict and Root (1) could not be modified to meet this need They have shown that the amount of the "Insensible Perspiration" bears a definite quantitative relationship to the metabolic rate under basal conditions They obtained the loss of weight per hour of subjects in the basal state by means of a delicate balance, sufficiently large to support the necessary weight, and plotted this against the basal calories for twenty-four hours, obtained by a standard method By so doing they found that the heat loss for a unit of time is a linear function of the insensible loss of weight for that interval of time They accordingly concluded that the twenty-four-hour basal heat production could be predicted from the hourly basal insensible loss of weight

The insensible loss of weight includes of necessity the water vapor eliminated from the body This vaporization of water is an important mechanism for the removal of heat If the insensible loss of weight bears a constant relationship to the heat elimination, it is necessary that two conditions be fulfilled (1) The organism must lose a fixed proportion of its heat by vaporization of water and (2) the weight of

[1] Aided by a grant from The Fellowship Corporation

water vapor must bear a fixed relationship to the total insensible loss of weight

Numerous studies of the proportion of the total heat eliminated, effected through the vaporization of water have been made by means of the calorimeter Soderstrom and Du Bois (2) point out the difficulties in determining accurately the water vapor given off, in the calorimeter, since the rate of ventilation may not always be sufficient to maintain a constant humidity They state that the error may be as much as 10 per cent The results they obtained with a group of normal men, some of the same men following the ingestion of food, a group of boys twelve to thirteen years old, and a group of old men,

TABLE 1

Percentage of heat loss effected through vaporization of water (Söderstrom and Du Bois)

Subject	Percentage of heat lost by vaporization	
	Average	Range
	per cent	*per cent*
Normal (13)	24	21–28
Normal—food (5)	23	21–26
Boys (8) 12–13 years	27	22–32
Old men (6)	27	23–29

will be found in table 1 The average percentage of heat lost through the vaporization of water for all groups varied only from 23 to 27

Likewise, Benedict (3) found in 43 observations of ten individuals in the basal state, an average value of 22 per cent, with a variation of 19 to 30 per cent He obtained the same value in ten experiments carried out with twenty individuals after the ingestion of food, with approximately the same variation

Levine and Wilson (4, 5) studied six normal children and found a variation of 24 to 29 per cent with an average value of 24 per cent of their total calories lost through the vaporization of water In the case of four normal and six marantic infants, they found 26 5 and 25 6 per cent respectively Their range for the whole group was only from 25 to 30 per cent These investigators point out that "Despite the enormous differences in metabolic rates in the age periods from

infancy to adult life, apparently a definite and unvarying fraction of the total amount of heat produced by all subjects was removed from the body by vaporization of water through skin and lungs, (average of 26 per cent) "

Since Isenschmid (6) has defined the insensible loss of weight as equal to the weight of the water vaporized plus the carbon dioxide excreted, minus the oxygen absorbed, it is clear that one may calculate the proportion of the total heat loss effected by the vaporization of water, if the insensible loss of weight, the carbon dioxide output, oxygen absorption and total heat production are known

TABLE 2

Relation between heat lost by vaporisation of water and total loss of heat in the basal state

Insensible loss	CO_2	O_2	Insensible water	Total heat		Heat loss by vaporization	
				Gasometric	Gravimetric		
grams per hour	*grams per hour*	*grams per hour*	*grams per hour*	*calories per 24 hours*	*calories per 24 hours*	*calories per 24 hours*	*per cent*
28 9	19 16	17 06	26 8	1,382	1,372	373	27
26 6	17 83	16 29	25 1	1 312	1,300	349	27
28 3	17 53	16 90	27 7	1,347	1,354	386	28
23 9	16 36	15 54	24 1	1,243	1,242	336	27
27 1	17 34	16 62	26 4	1,326	1 315	368	28
29 2	17 59	17 28	28 9	1 372	1,382	402	28
26 7	17 31	15 62	25 2	1,285	1,301	351	27
25 3	16 38	15 45	24 4	1,237	1,257	340	27
27 5	17 11	16 44	26 8	1,312	1 327	373	28

To do this, we determined the basal heat production, the oxygen absorption, and the carbon dioxide output by means of the Tissot method The basal insensible loss of weight was obtained by means of a large balance on the same day or alternate days The weight of the water vaporized was calculated from the equation of Isenschmid These data for a normal subject will be found in table 2 It will be seen that the heat lost by the vaporization of water (0 58 $\times$ weight of water vapor) bears a constant relationship (27 to 28 per cent) to the heat production, and therefore to the heat elimination, since the two are equal under these conditions

Our studies present further evidence that the organism tends to

lose a fixed proportion of its heat through the vaporization of water It is therefore true that the first condition necessary for constant relationship between the insensible loss of weight and the total heat elimination exists [2]

The second condition postulated, i e , that the weight of the water vapor must bear a fixed relationship to the total insensible loss of weight will now be considered From Isenschmid's equation, it is obvious that this relationship can only be disturbed by variation in the difference between the weight of carbon dioxide excreted and oxygen absorbed In the basal state, the respiratory quotient and consequently this difference, except in a few cases, varies but little Therefore, for individuals in the basal state, both conditions are fulfilled, and the insensible loss of weight must bear a definite relationship to the total heat elimination It is obvious that a marked departure from the usual basal quotient will entail a small error

The advantage of extending this simple method for the determination of total energy expenditure to consecutive twenty-four hour periods in the case of individuals who are taking food and voiding excreta, is obvious

On theoretical grounds, two major objections present themselves First, if the total heat elimination is to be used as a measure of the total energy expenditure, the performance of mechanical work must be avoided or measured Second, it will be recalled that the validity of this method rests upon the constancy of the relationship between the total insensible loss of weight, and the weight of water vaporized From Isenschmid's equation, it is obvious that this relation is effected by variations in the difference between carbon dioxide excreted and the oxygen absorbed In other words, the nature of the metabolic mixture will effect this relationship The degree to which it is effected may easily be calculated as follows An hypothetical individual has a basal metabolic rate of 2025 calories per twenty-four-hours The respiratory quotient is 0 82, under these conditions he will absorb 600 grams of oxygen and give off 676 grams of carbon dioxide The

[2] It will be further seen that these results confirm those of Benedict and Root in that the twenty-four hourly loss of heat predicted from the hourly insensible loss of weight agrees with the twenty-four hourly heat production determined by the Tissot method

weight of the water vapor given off may be calculated, since approximately 28 per cent[3] of the total heat loss is effected in this way The amount is 978 grams $\left(\frac{2025 \times 0\,28}{0\,58}\right)$ Therefore, the insensible loss of weight = 978 grams + 676 grams − 600 grams which is 1054 grams When, therefore, the respiratory quotient is 0 82, the weight of the water vaporized will be 92 8 per cent of the total insensible loss of weight. If the heat production remains the same, but the quotient *becomes 1 00 instead of 0 82, the individual will absorb 573 grams of oxygen and give off 788 grams of carbon dioxide* The insensible water remains the same Hence, the total insensible loss of weight becomes 1193 grams In this case, the weight of the water vapor becomes 82 per cent of the total insensible loss of weight

On the other hand, when the respiratory quotient is 0 707, the insensible loss of weight becomes 940 grams and therefore it will be seen that the weight of the water vapor is 104 per cent of the total insensible loss It is therefore theoretically true that an individual with a heat production of 2025 calories might lose insensibly an amount of weight which varies from 940 grams to 1193 grams What does this variation signify in terms of predicted heat loss? By consulting the table of Benedict and Root, it will be noted that each increment of one gram of the insensible loss of weight corresponds to thirty-one calories per twenty-four-hours The maximal variation in the insensible loss of weight for the subject whose heat production was 2025 calories, was 253 grams This would represent a variation of 315 calories per twenty four-hours, or 15 per cent of the total heat production When the usual basal respiratory quotient of 0 82 exists, the maximal variation from it to unity is 8 per cent, and from it to 0 707, 7 per cent Since Benedict and Root obtained the data for their table from subjects in the basal state, the respiratory quotients were presumably in the neighborhood of 0 82 Since neither pure carbohydrate nor fat furnish all the energy for the twenty-four-hour period, the possible error in the extension of Benedict's and Root's values to the twenty four-hour state would be less than 8 per cent The probable error is less than 5 per cent, the usual error allowable in other methods of determining energy outgo

[3] We have used the value obtained by us.

METHOD

If it is desired to obtain the weight of the insensible perspiration for twenty-four-hour periods in subjects who are taking food and voiding excreta, allowance must be made for the weight of these materials Under these circumstances the difference between the subject's weight at the beginning and at the end of the period is not merely the weight of the insensible perspiration, for the second weight of the subject has been "sensibly" increased by the weight of the ingesta and "sensibly" diminished by the weight of the urine and stool In

TABLE 3

Determination of insensible perspiration for a period of twenty four hours

	grams		grams
First weight of subject	61,695	Second weight of subject	61,465
Weight of food	1,615	Weight of urine	1,436
Weight of drink	715	Weight of stool	102
	64,025		63,003
First corrected weight			64,025
Second corrected weight			63,003
Insensible perspiration			1,022

Hourly insensible perspiration $\frac{1022}{24} = 42.6$

Total calories for the 24 hours = 1800

order to correct for these factors, the weight of the ingesta was added to the weight of the subject at the beginning of the period, and the combined weight of the urine and stool was added to the weight of the subject at the end of the period The difference between these corrected weights of the subject now represents the weight of the insensible perspiration for the period [4] Table 3 is an example of the application of this procedure for obtaining the total insensible loss

[4] This method of weighing the insensible perspiration, in the case of subjects who were active and taking food, has been used by a number of earlier observers Since their work has already been discussed in the paper of Benedict and Root (1) it is needless for us to review it again

of weight[5] The hourly insensible loss is obtained by dividing the total insensible loss by the length of the period expressed in hours The twenty-four hour calories, which correspond to this value, may be found by reference to the prediction table of Benedict and Root

In the use of this method it is necessary to guard against two major sources of error Benedict and Root pointed out the interfering effect of sweating on the one hand, and of lowering the skin temperature by undue exposure, on the other hand If water in the liquid state (sweat) leaves the body, weight will be lost but heat will not. The water must be evaporated in order to remove heat Hence an insen-

TABLE 4

Effect of sweating on insensible loss of weight

Date	Insensible loss per hour	Environmental temperature		Environmental humidity average 7 a.m. to 7 p.m.	Remarks
		Maximum	Average		
	grams	*F*	*F*	*per cent*	
June 29	69	62	60	98	Comfortable day
June 30	85	78	68	73	
July 1	92	82	73	72	Sweat drips from subject
July 2	99	82	75	74	Sweat drips from subject
July 3	80	86	78	78	Fan. No visible sweat
July 4	78	84	74	76	Fan. No visible sweat
July 5	70	77	66	70	Comfortable day

sible loss that includes sweat will be too great when used as a measure of heat loss Contrawise, when the skin is cold, less than the usual amount of heat will be removed by vaporization and the per cent of heat lost by that method will accordingly be less than the assumed amount Hence it is necessary that the subject be consciously neither hot nor cold The ideal skin temperature for this method of determining heat elimination has not yet been worked out

In order to study the influence of sweating, an obese but otherwise

[5] The subject was weighed by the "silk" scales (1), which is accurate to ten grams The excreta and drinking water were weighed on a balance accurate to one gram The individual items of food were weighed to one tenth gram, and the total for the day recorded to one gram

normal woman, was confined to bed for a number of days During this time persons were employed to watch her continuously so that we could be sure that no irregularities in our plan of investigation occurred The average of four determinations of the basal rate gave 1935 calories for twenty-four-hours During the period in question, the weather was cool the first day but became progressively hotter and wetter during the next four days The hourly insensible loss of weight was correspondingly higher on each succeeding day until a large electric fan was directed at the subject The unavoidable sweating which had been marked on July 1st and 2nd, ceased and the insensible loss of weight declined sharply The data will be found in table 4

TABLE 5

Effect of exposure on insensible perspiration

Date	Hourly insensible loss	Total calories for 24 hours predicted from insensible loss	Basal calories for 24 hours by Tissot method
	grams		
January 12	62 7	2,350	1,854
January 14	48 5	1,900	1,740
January 15	34 5	1,550	1,657
January 16	53 0	2,050	1,658
January 17	38 6	1,650	1,674
January 18	34 5	1,550	1,715
January 19	31 6	1,450	1,683

When the environmental temperature is low, the same per cent of heat is lost by evaporation provided the skin temperature is kept sufficiently high by means of clothing, but when the skin temperature, due to exposure, falls below the critical level (still to be determined) less than the usual amount of water is evaporated from its surface As a result, the relationship between insensible perspiration and total heat loss in the sense of Benedict and Root, no longer exists

The interference caused by exposure was very marked in the case of one of our subjects who was allowed to be up in a wheel chair She did not co-operate well and often was out of bed for more than an hour at a time with her legs entirely uncovered and the rest of her body insufficiently clad In her case, the prediction of total calories

from the insensible loss sometimes gave values less than the basal calories (table 5)

Some weeks later, when the basal calories were about 1550 for twenty four-hours, the same subject was confined to bed for three days under continuous guard Under these conditions the hourly insensible loss became an entirely satisfactory means of predicting the total heat loss, as will be seen by consulting table 6 The predicted total calories were 25 per cent greater than the basal calories

Under carefully controlled conditions, we have determined the insensible perspiration for a series of consecutive twenty-four hour periods

The subject was a normal man, thirty-two years old, who understood the nature of the investigation and whose co-operation was ideal.

TABLE 6

Total heat loss predicted from insensible perspiration when cooling of skin was prevented

Date	Hourly insensible loss	Total heat elimination
	grams	*calories for 24 hours*
April 24	45 6	1,900
April 25	47 0	1,930
April 26	46 8	1 930

In order to reduce the performance of mechanical work to a minimum, he was kept continuously in bed with the exceptions noted below He was clad in flanelette pajamas and socks The temperature of the room was kept close to 72°F during the day During the night a window was open The subject was allowed to sit up in bed during the day supported by a back rest He occupied himself reading, playing cards and chatting At 8 30 each morning he stepped out of bed to urinate into a weighed container and then walked to the scale a few feet away After being weighed, he returned to bed and took off his night clothes which were weighed and returned to him He kept his body warm with the bed covers in the interval As a rule, he was next taken to the laboratory by means of a wheel chair At such times he always had on a dressing gown and was protected from draughts by blankets In the laboratory he stepped from the chair

TABLE 7

Preliminary weighings needed to obtain total heat elimination for 24 hour periods

Date	Subject 8 40 a m	Food	Water	Urine	Stool	Remarks
1929	*grams*	*grams*	*grams*	*grams*	*grams*	
January 9	60,370	2,127	602	1,705	321	
January 10	59,360	2,359	688	1,495	106	
January 11	59,520	2,459	268	1,527	122	
January 12	59,385	2,356	724	2,180	0	
January 13	59,210	2,356	300	1,194	0	
January 14	59,590	2,355	368	1,376	22	Restless night
January 15	59,740	2,356	407	1,504	205	
January 16	59,785	2,044	290	1,585	187	
January 17	59,260	2,043	234	1,176	131	
January 18	59,235	2,045	202	1,382	107	
January 19	59,000	2,045	143	1,301	124	
January 20	58,765	2,045	474	1,557	0	
January 21	58,735	2,044	197	1,340	162	
January 22	58,500	2,046	103	1,270	119	
January 23	58,325	2,043	173	1,163	0	
January 24	58,370	2,046	310	1,650	159	
January 25	58,040	2,044	223	1,514	0	
January 26	57,790	2,041	75	1,108	0	
January 27	57,840	2,044	283	1,350	113	
January 28	57,725	2,044	119	1,156	147	
January 29	57,440	2,044	68	959	0	
January 30	57,465	2,060	159	1,206	0	
January 31	57,480	2,068	193	1,111	105	
February 1	57,515	2,042	147	1,422	0	
February 2	57,245	2,046	0	1,334	85	
February 3	56,815	2,044	166	905	0	
February 4	57,100	2,044	88	1,236	188	
February 5	56,875	2,046	74	985	0	
February 6	56,940	2,044	121	1,340	0	
February 7	56,815	2,044	249	1,257	0	
February 8	56,930	2,046	200	1,360	300	
February 9	56,585	2,043	134	1,308	60	
February 10	56,435	2,046	430	1,696	0	
February 11	56,345	2,044	73	1,274	0	
February 12	56,310	2,045	86	1,180	361	
February 13	55,960	2,045	0	1,132	0	
February 14	55,980	2,043	117	1,326	0	
February 15	55,975	2,034	43	1,106	288	

to the bed attached to the delicate balance in order to permit the determination of the insensible loss in the basal state or to measure

TABLE 8

Predicted heat elimination for 24 hour periods

Date	Corrected weight		Insensible loss		Total calories predicted
	I	II	Total	Hourly	
1920	grams	grams	grams	grams	
January 9	63,099	61,386	1 713	71 4	2 630
January 10	62,407	61 121	1,286	53 6	2,130
January 11	62,247	61,034	1,213	50 5	2 040
January 12	62 465	61,392	1,073	44 7	1,860
January 13	61 862	60,784	1 078	44 9	1,870
January 14	62,313	61,138	1,175	49 0	1,990
January 15	62 503	61 494	1 009	42 0	1 775
January 16	62,119	61,032	1,087	45 3	1,880
January 17	61,537	60 542	995	41 5	1,760
January 18	61,482	60 489	993	41 5	1,760
January 19	61 188	60 190	998	41 6	1,760
January 20	61 284	60,292	992	41 0	1,745
January 21	60 976	60 002	974	40 6	1,740
January 22	60,649	59 714	935	39 0	1,680
January 23	60 541	59 533	1,008	41 6	1,760
January 24	60 726	59,849	877	36 5	1 610
January 25	60 307	59 304	1 003	41 7	1,760
January 26	59,906	58 948	958	39 9	1 715
January 27	60 167	59,188	979	40 8	1,730
January 28	59,888	58 743	1,145	47 7	1,950
January 29	59,552	58 424	1 128	47 0	1,930
January 30	59,684	58,686	998	41 6	1 760
January 31	59,741	58,731	1,010	42 1	1,780
February 1	59 704	58 667	1 037	43 1	1,815
February 2	59,291	58 234	1,057	44 0	1,840
February 3	59,025	58 005	1 020	42 5	1,790
February 4	59 232	58,299	933	38 8	1,680
February 5	58,995	57 925	1,070	44 5	1 855
February 6	59 105	58,155	950	39 6	1,705
February 7	59 108	58 187	921	38 3	1,665
February 8	59 176	58 245	931	38 8	1,680
February 9	58 762	57 798	964	40 2	1 720
February 10	58 911	58 041	870	36 3	1 600
February 11	58 462	57,584	878	36 6	1,610
February 12	58 441	57 501	941	39 2	1,700
February 13	58,005	57 112	893	37 2	1 630
February 14	58 140	57 296	844	35 2	1,570
February 15	58 052	57,064	988	41 0	1,745

the basal metabolic rate by the Tissot method Thereafter he was taken back to bed and remained there until the next morning except when he got up to urinate or defecate The weights of the food, water, urine and stool for each twenty-four-hour period, were recorded to one gram

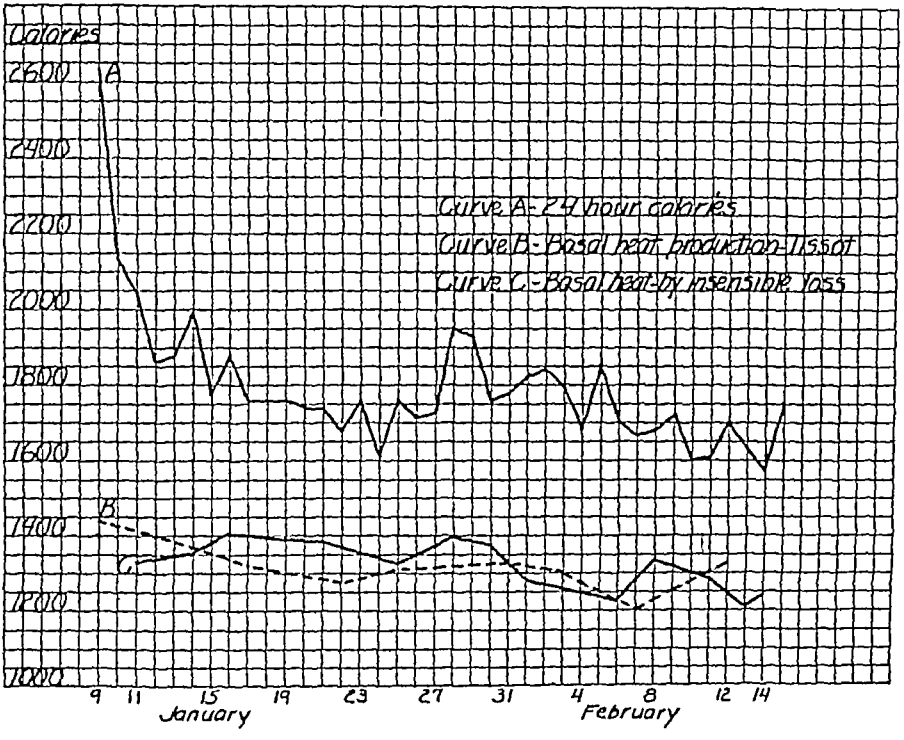

FIG 1 SHOWS THE CLOSE AGREEMENT BETWEEN BASAL METABOLIC RATE DETERMINED BY THE TISSOT METHOD (BROKEN LINE *B*) AND CALCULATED FROM THE HOURLY INSENSIBLE LOSS OF WEIGHT (SOLID LINE *C*)

The upper line A shows the total twenty-four hourly heat production obtained by means of the insensible loss

The data of the last period of this study are presented in detail The period began at 8 40 a m on January 9 and ended at 8 40 a m on February 16, 1929 From January 9th through January 15th the subject received a diet containing 2091 calories and intended to furnish the energy required for maintenance Thereafter the diet contained 1078 calories The daily record of the weights of the subject and of

the "sensible" ingesta and excreta are contained in table 7 Table 8 contains the corrected weight of the subject at the beginning and end of each twenty-four-hour period The subtraction of the second from the first corrected weight gives the insensible loss for each twenty-four-hours (column 4) In order to conform to the prediction table of Benedict and Root this has been converted into "loss per hour " In the last column the total heat eliminated, predictable from the hourly insensible loss, has been set down

In figure 1, the total twenty-four-hourly heat elimination is plotted together with the basal calories for twenty-four-hours obtained by the Tissot method It will be seen that in general the total heat elimination shows the expected relationship to the basal metabolic rate It is roughly 30 per cent greater That is about the difference one anticipates between the total and basal calories for persons in bed In the middle of the period (January 29 to January 30) there is an increase in both total and basal heat production At this time the subject was visited by a person of the opposite sex in whom he had a deep interest

It is further interesting to note the rapid fall in total heat production during the first three days in bed It is apparent that during this time he accustomed himself to the enforced quiet From then on, the maximal variation in total calories was 420 calories which represents approximately 25 per cent of his average outgoing calories It is not unreasonable to believe that under these conditions, this variation may be entirely accounted for by different amounts of activity Since there was a declining heat production coincident with a decrease in weight, this variation becomes less significant

This series of observations demonstrates the applicability of this method to the determination of the total twenty-four-hourly heat elimination

CONCLUSIONS

The statement of Benedict and Root that the basal metabolic rate may be accurately predicted from the basal insensible loss of weight has been confirmed

The principle has been modified so that it may be satisfactorily used to measure the total heat production of human subjects, if pre-

cautions are taken to prevent either sweating or cooling of the skin below the critical temperature

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MEASUREMENT OF TOTAL WATER EXCHANGE[1]

By L. H. NEWBURGH MARGARET WOODWELL JOHNSTON AND MARK FALCON LESSES

(From the Department of Internal Medicine, Medical School, University of Michigan, Ann Arbor)

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As a rule when the terms, "water balance" or "water exchange," occur in clinical literature, the writer has in mind merely a comparison between the water which enters the body as food and drink with the water which leaves it as urine Sometimes the water of the stool is also included A statement that includes merely these increments of water is inaccurate and liable to be misleading, since it fails to take into account (1) the large amount of water that is evaporated from the skin and lungs, (2) the water that is formed by oxidation of the food, (3) water physically held as part of the protoplasm, but set free when the organism derives some of its energy by burning its own tissues

I

We propose to describe a system which permits the observer to obtain an accurate account of all the sources and the total amount of water that becomes available for the organism on the one hand and of the amount of water that leaves the organism on the other hand

In working out a plan for dealing with all the increments of water, it is helpful to think of them under two separate headings (1) Those that may be measured by standard laboratory methods, and (2) those whose value is obtained indirectly by calculation The first group includes the water that the subject drinks as such, and the water contained in the food, urine and stool The second group consists of the water evaporated from the skin and lungs, the water that is a byproduct of the combustion of materials, and water made free when body tissue is burned

[1] Aided by a grant from The Fellowship Corporation.

In order to determine whether the organism has gained or lost water, it is necessary to classify the above mentioned portions of water under two headings On one side of the balance sheet are gathered together all those increments of water that have become available as free water for the first time during the period They include not only the water that enters the organism from the outside, but also the water formed by oxidation of the metabolic mixture,[2] and the water that is freed when body tissues are burned (preformed water) On the other side of the balance sheet all the fractions of water that have been given off by the organism, are brought together They are the water of the urine and stool and the water that has been given off by

TABLE 1

Water exchange

Available water		Water given off	
	grams		*grams*
A Water drunk	——	E Water of urine	——
B Water of food	——	F Water of stool	——
C Water of oxidation	——	G Insensible water	——
D Preformed water	——		
Total	——	Total	——
		Difference ——	

the skin and lungs[3] (insensible water) Table 1 is a water balance form that was found useful

The weights of each of these seven items of water were obtained in the following manner

A The subject drank water as desired from a "thermos bottle" fitted with a rubber stopper containing a glass drinking tube The stoppered bottle filled with cold water was weighed at the beginning of the period and again at the end on a balance accurate to one gram Less than one gram of water evaporated from the bottle in twenty-four hours

B Several different diets were used The best results were obtained when only milk and sucrose was fed During this period, the

[2] The metabolic mixture consists of all the materials burned by the organism during the period and thus often includes body tissues

[3] This water is chiefly or entirely removed from the body by evaporation, but it also includes any water lost as liquid sweat

desired composition was secured by mixing appropriate amounts of cream (40 per cent), whole milk and skim milk After thorough mixing a sample was removed Its water content was determined by freezing and desiccation in vacuo (1) The sucrose was considered to be dry

At other times the diet included bread, butter and bananas in addition to the milk mixture and sugar Samples of banana were frozen and desiccated The water content of the bread was determined by drying in the oven Since the butter contained, at most, two grams of water, its water was not regularly determined Fifteen per cent of its weight was allowed for water [4]

Finally we were interested to know what results could be obtained when the usual types of food were employed instead of the highly

TABLE 2

Insensible water

I		II	
	grams		*grams*
Subject at beginning	——	Subject at end	——
Food	——	Urine	——
Drink	——	Stool	——
Oxygen	——	Carbon dioxide	——
Total	——	Total.	——

restricted diets just described Accordingly the standard vegetables, fruits, meats, milk, eggs, bread and butter cooked in the customary way, were fed Complicated desserts and salad dressings were omitted Since it seemed hopeless to obtain a fair sample from such a complicated mixture, the water content was determined as follows A dietitian prepared two diets as nearly alike as she could All that the subject was to receive at any meal was placed on a tray and the whole weighed After the subject had eaten, the tray and dishes were weighed again The duplicate diet was also placed on a tray which was then weighed The food was next scraped into an enameled can of known weight, and the covered can was placed in a refrigerator

[4] In order to get accurate knowledge of the composition of the diet, a sample of the milk mixture was analysed for nitrogen (Kjeldahl), fat by the Babcock method, and ash Samples of the dry bread and bananas were analysed for nitrogen.

The subject received three meals daily and the duplicate diet was also served in three portions, weighed and collected in the can The latter was then weighed with the whole wet duplicate diet in it and placed on a steam bath whose temperature varied from 50° to 70°C It took about two weeks to reach its final weight The loss was assumed to have been caused entirely by evaporation of water However such "dry" diets[5] lost an additional small amount of weight after being in a desiccator over sulphuric acid

TABLE 3

Constants to obtain oxygen absorbed and carbon dioxide given off

Oxygen	
Multiply protein	by 1 38
Multiply fat	by 2 86
Multiply carbohydrate	by 1 13
Carbon dioxide	
Multiply protein	by 1 46
Multiply fat	by 2 78
Multiply carbohydrate	by 1 54

C The weight of the water that arises from protein, fat or carbohydrate when they are oxidized by the organism, has been determined by several students We used the following values (2)

100 grams protein	yields 41 grams H_2O
100 grams fat	yields 107 grams H_2O
100 grams carbohydrate	yields 60 grams H_2O

It is, however, necessary to know the metabolic mixture before this increment of water can be calculated The method of calculating the former has already been described (3)

D To obtain the preformed water the diet and the metabolic mixture are compared When the former contains more energy than the latter and when no body protein is destroyed or when the caloric value of the two is the same, no preformed water is released When, however, a submaintenance diet is fed, the destruction of body tissues frees the water that was physically held by them But under

[5] All of the dry duplicate diet collected during a period was ground and a sample analysed for nitrogen

TABLE 4

Weight of oxygen added to body to complete oxidation of metabolic mixture

A *Protein* (Muscle protein)

Composition (4)

C = 51 per cent { Respiratory 40 per cent / Urine and feces 11 per cent

H to form water = 4 8 per cent

O = 21 per cent

1 gram C requires 2 66 grams O to form CO_2

1 gram C requires 1.33 grams O to form urea

1 gram H requires 8 0 grams O to form water

therefore

(a) Protein × (0 40 × 2.66) = O to form CO_2

(b) Protein × (0 11 × 1.33) = O to form urea

(c) Protein × (0 048 × 8 0) = O to form H_2O

(d) Protein × 0 21 = intramolecular O

(a + b + c) − (d) = 1.384, hence

Protein × 1.38 = Oxygen added

B *Fat* (tripalmitin)

Composition

C = 76 per cent

H = 12 per cent

O = 12 per cent

(a) Fat × (0 76 × 2 66) = O to form CO_2

(b) Fat × (0.12 × 8 0) = O to form H_2O

(c) Fat × 0 12 = intramolecular O

(a + b) − (c) = 2 86, hence

Fat × 2 86 = Oxygen added

C *Carbohydrate* (sucrose)

Composition

C = 42 per cent

H = 6.5 per cent

O = 51.5 per cent

(a) CH × (0 42 × 2 66) = O to form CO_2

(b) CH × (0 065 × 8 0) = O to form H_2O

(c) CH × 0 515 = intramolecular O

(a + b) − (c) = 1 125 hence

Carbohydrate × 1 13 = Oxygen added

Weight of carbon dioxide yielded by the metabolic mixture

A *Protein*

Protein × (0 40 × 3 66) = CO_2

B *Fat*

Fat × (0 76 × 3 66) = CO_2

C *Carbohydrate*

CH × (0 42 × 3 66) = CO_2

these circumstances the total amount of preformed water released can not be calculated while glycogen is being destroyed, since it is not known how much water it binds In the previous paper (3) we pointed out the ways by which we believed we had selected periods during which no glycogen (or a very few grams) was being oxidized

Comparison between the ingoing and outgoing nitrogen shows whether body protein has been destroyed It is customary to allow three grams of preformed water for every gram of protein The remainder of the calories furnished by the body come from fat Its preformed water is considered to be about ten per cent of its weight

E The water content of the urine was obtained by freezing and desiccating, in vacuo, duplicate samples of each twenty-four hourly amount, by means of the same technique employed for milk

F The subject defecated directly into a weighed enameled container by means of a commode After recording the weight of the container plus the wet stool, the whole was placed on the steam bath without transfer The loss of weight, which was complete in three or four days, was assumed to be entirely due to evaporation of water [6]

G We have obtained the weight[7] of the insensible water by adding

[6] All of the feces formed while any single diet was being used was mixed, ground and analysed for nitrogen When the subject received only the milk mixture and sugar, fat and fecal ash was also determined

[7] Since the time of Sanctorius (1614) it has been known that there is a continuous loss of gaseous material from the body Later studies have shown that this consists of carbon dioxide and water vapor The combined weight of these two is greater than the weight lost by the organism as determined by the scales (The terms "Insensible loss" or "Insensible perspiration" refer to the latter) This is true because the loss of weight caused by the outward passage of carbon dioxide and water, is, in part, compensated for, by the weight of the oxygen absorbed

Isenschmid (5) has expressed this relationship thus

$$\text{Insensible loss} = H_2O + CO_2 - O_2$$

If carbohydrate alone were being burned the weight of oxygen absorbed would equal the weight of the oxygen contained in the carbon dioxide given off Under these conditions the insensible loss would equal the weight of the water plus carbon

When, as is usually the case, fat and protein are burned, some of the oxygen absorbed is used to complete the oxidation of hydrogen as well as carbon Then the insensible loss may be thought of as made up of water, carbon and hydrogen Schwenkenbecher and Inagaki (6) pointed out this relationship in 1905

Because of this varying relationship it is not possible to determine the total

the weight of everything that entered the body during the period to its weight at the beginning, and by adding the weights of everything that left the body during the period, other than water vapor, to its weight at the end of the period The difference between the two sums is clearly the weight of the water lost insensibly Table 2 shows what weights need to be used The manner of obtaining the weights of the subject, food, drink, urine and stool, has already been described

The weight of the oxygen is obtained by calculating how much of it had to be added to the body to complete the oxidation of the metabolic mixture, and the weight of the carbon dioxide is derived by means of the same type of calculation The time required for these cumbersome calculations may be greatly reduced by means of numerical constants

Table 3 shows the constants[8] we have used These constants were obtained by the calculations shown in table 4

II

When it was desired to obtain the day to day water exchange of an individual we proceeded as follows

1 The mean twenty four hourly heat production was determined (3)

2 The metabolic mixture was calculated from this value, the composition of the diet and the outgoing nitrogen

3 Next the weights of the oxygen absorbed and carbon dioxide given off on the basis of this mixture were obtained, and the oxygen value subtracted from that for carbon dioxide

4 The subtraction of this latter difference from each twenty four hourly insensible loss gives the weight of the water lost insensibly during each twenty-four hours

5 The water formed by oxida ion of the metabolic mixture was calculated

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insensible water by merely deducting the weight of the carbon of the metabolic mixture from the insensible loss. The oxygen and carbon dioxide may be determined directly or calculated from the metabolic mixture With the weights of the insensible loss, the carbon dioxide and oxygen, the insensible water may be obtained from Isenschmid's Equation

[8] Lusk (Science of Nutrition 3rd ed., p 28) states that it requires 133 43 grams oxygen to burn 100 grams meat protein, 288 5 grams oxygen for 100 grams fat, and 118 5 grams oxygen for 100 grams starch

6 The diet was compared with the metabolic mixture and the differences used to calculate preformed water, if body tissue was being oxidized, or if tissue was being added to the body, the appropriate amount of water (stored by it) was subtracted from the total available water

The use of an average metabolic mixture for the period instead of calculating one for each twenty-four hours has two advantages It tends to compensate for any irregularities of absorption and oxidation and so probably gives a better statement of what has been metabolized Further, it greatly reduces the time required for calculation

III

A concrete example of the way in which water exchange was determined will now be given

The normal subject and the general conduct of the study have already been described (3) From January 3 to January 8, 1929, his life and diet were unrestricted The evening of January 8 he went to bed in the special room, and the next morning began to receive a milk mixture and sugar in amounts which were expected to be close to his requirement for maintenance

The water exchange was determined for five consecutive days beginning January 11 During this time the milk mixture was found by analysis to contain 69 grams of protein, 83 grams of fat and 112 grams of carbohydrate, per day In addition he received 155 grams of sucrose daily The average twenty-four hourly heat production was 1907 calories The diet yielded 2091 calories, and he destroyed 11 88 grams of body protein daily The subtraction of the out-going calories from the calories of the diet plus those of the body protein, left 232 calories to be stored For purposes of calculation it is assumed that they are stored as fat This represents the storage of 24 grams of fat, or an addition to the body weigh' of 26 grams On the other hand he lost 11 9 grams of protein from the body daily, which, with its water, represents a loss of 48 grams Therefore, he should lose 22 grams of weight daily His metabolic mixture was 81 grams protein (diet plus body protein), 267 grams carbohydrate (it is assumed that all the carbohydrate of the diet was burned), and 57 grams of fat (to supply the difference between the outgoing calories and the sum of the

calories derived from the protein and carbohydrate oxidized) From the above it is evident that there was released the water which was held by the 11 9 grams of body protein destroyed daily That is an addition of 36 grams to the available water On the other hand he stored 24 grams of fat which holds 2 grams of water, so that we may consider that 34 grams of preformed water became available

The water formed by the oxidation of this metabolic mixture (ob tained by means of the constants mentioned above) was 254 grams

By means of the constants in table 3 it is found that the oxygen absorbed to complete the oxidation of the metabolic mixture weighed 576 5 grams and the carbon dioxide produced weighed 687 9 grams The difference is 111 grams The subtraction of this value from the twenty-four hourly insensible loss gives the daily insensible water

Since the diet was unusual it was thought that the standard method of calculating the available calories of the diet might not be sufficiently accurate For this reason the calories actually lost in the stool were determined by the oxy calorimeter of Benedict and Fox[9] (7) The calories lost in the urine were calculated by multiplying the urinary N by 8, (following the custom of the Carnegie Institution) The caloric value of the stool was 4 35 calories per gram of dry weight The total calories lost in the stool and urine for the period were 979 or 196 per day The full heat value of the diet was obtained by multiplying protein by 5 65, fat by 9 54 and carbohydrate by 4 To this value was added the calories derived from body protein, making a total of 2317 daily From this must be substracted the calories lost in urine and stool, leaving 2121 calories for metabolic disposal The twenty-four hourly calories determined by insensible loss were 1907

Since the full heat value has been assigned to the materials oxidized, the calories of the metabolic mixture in this case must consist of the total heat production plus the potential heat lost in the urine and stool, that is, 1907 + 196 = 2103 The metabolic mixture would accordingly be protein 81 grams, fat 61 grams and carbohydrate 267 grams The only difference between the metabolic mixtures calculated by the two methods is four grams of fat With the latter mix-

[9] We are indebted to Dr T M Carpenter of the Nutrition Laboratory of the Carnegie Institution for this determination.

TABLE 5

Data used in calculation of water exchange

Date	Weight of subject 8 40 a.m	Water	Milk*		Urine			Stool			Insensible loss	Heat production
			Total	Water	Total	Solids	N	Total	Solids	N		
1928	*grams*	*grams*	*grams*	*per cent*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*calories*
January 11	59,520	268	2,299	87 8	1,527	45	12 04	122	17 5	0 72†	1 213	2,040
January 12	59,385	724	2,200	87 5	2,182	49 6	12 33	0		0 72	1,073	1,860
January 13	59,210	300	2,198	87 5	1,194	44 6	12 69	0		0 72	1,078	1,870
January 14	59,590	368	2,201	87 5	1,376	41 7	11 76	22	6 5	0 72	1,175	1,990
January 15	59,740	407	2,200	87 3	1,504	42 6	11 60	205	55	0 72	1,009	1,775
January 16	59,785											

* To obtain total weight of food, add 155 grams daily for sucrose

† Total mixed stool analysed in duplicate for N and apportioned per day

TABLE 6

Water exchange of a normal subject Diet more than maintenance

Date	(1) Drink	(2) Food water	(3) Preformed water	(4) Oxidation water	(5) Water of urine	(6) Water of stool	(7) Insensible water	(8) Available water	(9) Outgoing water	(10) Water balance
Available energy of diet calculated by standard method										
	grams	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	
January 11	268	2,018	34	254	1,482	105	1,102	2,574	2,689	−115
January 12	724	1,925	34	254	2,132		962	2,937	3,094	−157
January 13	300	1,923	34	254	1,149		967	2,511	2,116	+395
January 14	368	1,926	34	254	1,334	16	1,064	2,582	2,413	+169
January 15	407	1,921	34	254	1,461	150	898	2,616	2,509	+107
Available energy of diet calculated from full heat value of food, stool and urine										
January 11	268	2,018	34	259	1,482	105	1,101	2,579	2 688	−109
January 12	724	1,925	34	259	2,132		961	2 942	3,093	−151
January 13	300	1,923	34	259	1,149		966	2,516	2,115	+401
January 14	368	1,926	34	259	1,334	16	1,063	2,587	2,412	+175
January 15	407	1,921	34	259	1,461	150	897	2,621	2,508	+113

ture the predicted daily loss of weight would be 24 grams instead of 22 grams as in the former case

The remaining data needed to obtain the water exchange are shown

in table 5 With this information at hand, the values set forth in table 6 were secured Columns 1, 2, 3 and 4 show the amounts of the various increments that make up the available water (column 8) Columns 5, 6 and 7 are the separate items of outgoing water, brought together in column 9 Finally column 10 shows how much water has been retained or lost by the organism during each 24 hours The table also shows the effect on water exchange of each of the two ways of calculating the heat value of the diet It is clear that the differences are not significant [10]

IV

In order to estimate the degree of accuracy of this method for obtaining water exchange, a prediction of the water retention or loss for this same period has been made This was done by comparing the actual change in weight with the theoretical loss of weight and assuming the difference to be water See table 7 In the upper section of the table, the caloric value of the diet is calculated by means of the usual heat values assigned to food In the lower section the caloric value of the diet is obtained by subtracting the calories lost in urine and stool from the full heat value of the diet It is noticeable that a marked discrepancy between the predicted and determined water balance exists on the last day, but by both methods of calculation the agreement is surprisingly good for the other four days One may conclude from this comparison that the usual caloric values assigned to food are sufficiently accurate to give excellent values for water balance The reason for the error on the last day is not evident, but it has been consistently noticed that on days when an unusually large stool was voided the largest errors in water balance have occurred. It should be pointed out, however, that the total error for the five days was 44 grams or a little more than 8 grams per day

Table 8 gives a comparison between the predicted and determined water balance when the normal subject was receiving a somewhat more complicated diet than the one just dealt with In addition to the milk mixture and sucrose he was given bread, butter, bananas and

[10] The heat value of the stool calculated from determinations of nitrogen, fat, ash and carbohydrate by difference, was 4 4 calories per gram of dry weight This checks well with the value 4.35 obtained by the oxy calorimeter

grape-nuts This diet, like the one taken during the period represented by table 7, also contained more energy than the maintenance requirement This period followed one during which the subject was living under the special conditions of the investigation except that he was allowed the "house diet" The data for calculating the water balance of this period will be found in table 1 of the appendix

The water balance of a third period of moderate overnutrition is shown in table 9 The diet contained milk, sucrose, bread, butter

TABLE 7

Comparison between predicted and determined water balance based on data in table 6

Date	Change in subject's weight	Theoretical loss	Water balance		
			Predicted	Determined	Error
	grams	*grams*	*grams*	*grams*	*grams*
January 11	−135	22	−113	−115	2
January 12	−175	22	−153	−157	4
January 13	+380	22	+402	+395	7
January 14	+150	22	+172	+169	3
January 15	+45	22	+67	+107	40
Totals			+375	+399	
January 11	−135	24	−111	−109	2
January 12	−175	24	−151	−151	0
January 13	+380	24	+404	+401	3
January 14	+150	24	+174	+175	1
January 15	+45	24	+69	+113	44
Totals			+385	+429	
Error for period 44					

and bananas, but the "grape-nuts" were not used This period followed one of undernutrition during which there had apparently been a depletion of glycogen since the fasting respiratory quotient had fallen to 0 72 from the earlier level of 0 82 When the higher diet of this third period of overnutrition was taken by the subject, his quotient again rose to 0 82, indicating that he had replaced the glycogen destroyed in the preceding period However, when calculating the metabolic mixture used in compiling table 9, it was assumed that the extra calories of the diet were stored as fat It is instructive

to see how much difference in water exchange would be caused by using a metabolic mixture based on the assumption that all the extra calories were stored as glycogen The metabolic mixture in the first case was protein 66 grams, fat 76 grams, carbohydrate 270 grams In the second case it would be protein 66 grams, fat 88 grams, carbohydrate 243 grams The change in metabolic mixture would affect the water of oxidation, the insensible water and the preformed water Since the preformed water held by glycogen is not known, we have left

TABLE 8

Comparison between determined and predicted water balance in overnutrition

Date	Change in subject's weight	Theoretical loss	Water balance		
			Predicted	Determined	Error
1925	*grams*	*grams*	*grams*	*grams*	*grams*
November 13	−475	22	−453	−433	20
November 14	−175	22	−153	−161	3
November 15	−470	22	−448	−402	46
November 16	+415	22	+437	+423	14
November 17	+85	22	+107	+133	26
November 18	−20	22	+2	−31	33
November 19	−350	22	−328	−275	53
November 20	+225	22	+247	+255	8
November 21	−10	22	+12	+7	5
November 22	+190	22	+212	+229	17
November 23	−125	22	−103	−106	3
Totals			−468	−361	
Error for period 107					

all of the preformed water out of the following calculation While this obviously fails to give a true statement of the water exchange, it does not affect the relationship between the predicted and determined water balance This is true because the predicted loss of weight as ordinarily calculated includes the preformed water which also makes up part of the available water This fact comes out clearly when the two balances are compared by means of algebraic equations

(1) Predicted water balance = (Solids + Preformed Water) ± (Change in weight)

(2) Determined water balance = (Preformed water + Drink + Food Water + Oxidation water) − (Outgoing water)

If our predicted and determined balances are correct, then

Predicted water balance = Determined water balance

Therefore

(Solids + Preformed water) ± (Change in weight) = (Preformed water + Drink + food water + Oxidation water) − (Outgoing water)

Hence

(Solids) ± (Change in weight) = (Drink + Food water + Oxidation water) − (Outgoing water)

TABLE 9

Comparison between determined and predicted water balance when glycogen is being stored

Date	Change in subject's weight	Theoretical loss	Water balance		
			Predicted	Determined	Error
1928	*grams*	*grams*	*grams*	*grams*	*grams*
December 3	+145	−15	+160	+173	13
December 4	+520	−15	+535	+527	8
December 5	−150	−15	−135	−118	17
December 6	−50	−15	−35	−7	28
December 7	−25	−15	−10	−26	16
December 8	−80	−15	−65	−52	13
Totals			−497	−450	
Error for period 47					

A detailed statement of the water exchange for the period under consideration, showing the effect of each metabolic mixture, will be found in table 10 Consideration of table 10 brings out several points of interest (1) If one is trying to account for the difference between the actual weight of an individual and what he would be expected to weigh as the result of any given diet, the discrepancy, due to retention or loss of water, may be determined as successfully when preformed water is left out of the account as when it is included

TABLE 10

Water exchange

A When the extra calories of the diet are stored as fat and the metabolic mixture is protein 66 grams fat 76 grams, carbohydrate 270 grams

Date	Food water	Drink	Preformed water	Oxidation water	Available water	Water of urine	Water of stool	Insensible water	Outgoing water	Determined balance	Actual change in weight	Predicted change in weight	Predicted balance
	grams	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*
December 3	1 484	552	19	270	2 326	1 100	143	909	2 152	+173	+145	−15	+160
December 4	1 484	838	19	270	2 612	1 060	0	1 024	2 084	+527	+520	−15	+535
December 5	1 491	455	19	270	2 236	1 205	75	1 073	2 353	−118	−150	−15	−135
December 6	*1 491*	*962*	*19*	*270*	*2 743*	*1 474*	*124*	*1 151*	*2 749*	*−7*	*−50*	*−15*	*−35*
December 7	1 490	502	19	270	2 282	1 171	0	1 136	2,307	−26	−25	−15	−10
December 8	1 484	612	19	270	2 390	1 070	110	1 261	2 441	−52	−80	−15	−65
										+497			+450

B When the extra calories of the diet are stored as glycogen and the metabolic mixture is protein 66 grams fat 88 grams carbohydrate 243 grams

December 3	1,484	552		267	2 303	1,100	143	909	2,164	+139	+145	+20	+125
December 4	1 484	838		267	2 589	1 060	0	1 024	2 096	+493	+520	+20	+500
December 5	1 491	455		267	2 213	1 205	75	1 073	2 365	−152	−150	+20	−170
December 6	1 491	962		267	2 720	1 474	124	1 151	2 761	−41	−50	+20	−70
December 7	1 490	502		267	2 259	1 171	0	1 136	2 319	−60	−25	+20	−45
December 8	1,484	612		267	2 367	1 070	110	1 261	2,453	−87	−80	+20	−100
										+292			+240

A Preformed water is included in the calculation in the usual manner

B Preformed water is not included in either the available water or in the predicted loss of weight.

This is demonstrated in figure 1, which represents that period[11] in the study of the normal subject, when the preformed water was the largest, namely 65 grams daily The solid line (*A*) is the predicted weight when the predicted loss is only the weight of protein and fat destroyed, and the broken line (*B*) is the predicted weight when the

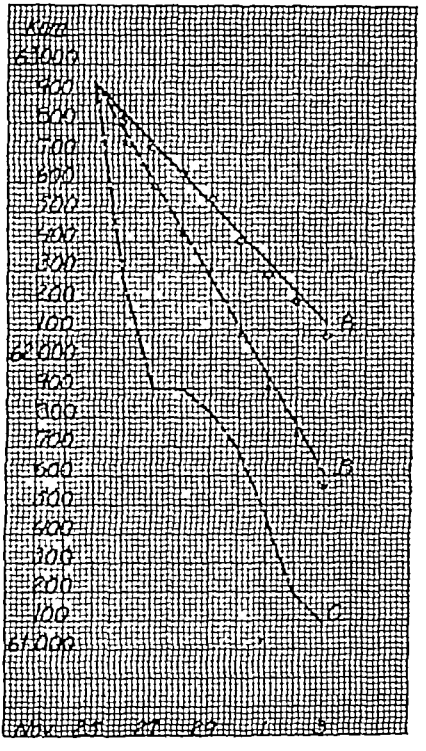

FIG 1

C, actual weight of subject $B - -$, and $B \times \times$, predicted and corrected weight obtained in usual way $A -$, and A o o, predicted and corrected weight when no preformed water is included in the calculation

predicted loss of weight includes the preformed water in addition to the protein and fat The circles and crosses indicate the subject's real weight (*C*) corrected each day by adding or subtracting the amount of water that had been held or lost by the subject But in

[11] Not the same period as used for Table 10 It was the first period of undernutrition and immediately preceded that presented in table 10

the case of the corrections represented by the circles, the water balances used to make the corrections were the differences between the outgoing water and the available water when the latter did not include the preformed water Hence both the predicted loss of weight (A) and the water balance are reduced to the same degree This corrected weight is as close to the predicted weight when preformed water is not considered as when it is The difference between the determined and predicted water balance is, in each case, 46 grams for the whole period of 8 days

TABLE 11

Comparison between predicted and determined water balance in undernutrition

Date	Change in subject's weight	Theoretical loss	Water balance		
			Predicted	Determined	Error
1929	*grams*	*grams*	*grams*	*grams*	*grams*
January 16	−525	100	−425	−404	21
January 17	−25	100	+75	+78	3
January 18	−235	100	−135	−135	0
January 19	−235	100	−135	−138	3
January 20	−30	100	+70	+64	6
January 21	−235	100	−135	−124	11
January 22	−175	100	−75	−76	1
January 23	+45	100	+145	+129	16
January 24	−330	100	−230	−214	16
January 25	−250	100	−150	−166	16
Totals			−985	−966	

Error for period 19 grams

(2) It is also desirable to realize that the errors in water balances found in table 10 are largely attributable to something other than an incorrect statement of the metabolic mixtures, since the errors between the predicted and determined balances are essentially the same even though the fat and carbohydrate values of the two metabolic mixtures are different.

The period represented in figure 1, was the first period of undernutrition in which water exchange was studied The data will be found in table 3 of the appendix That the underfeeding caused

destruction of glycogen is clearly indicated by the fall of ten points in the respiratory quotient It was, however, assumed, when constructing the metabolic mixture, that all of the endogenous calories came from protein and fat The water balance thus obtained indicates that the organism lost 695 grams of water during the first two days Most of this water was presumably released by the destruction of glycogen If the latter has the same hydrophylic coefficient as protein, the water loss would indicate that about 200 grams of glycogen had been destroyed

The next period, like the one represented by figure 1, also shows the effect of the first days of undernutrition with a probable destruction of glycogen It also followed an interval during which the subject

TABLE 12

Comparison of three periods of undernutrition in which carbohydrate in diet differed

Period	Date	Protein	Fat	Carbo hydrate	Diet calories	Total nitrogen out	Heat production	Average fasting R Q
		grams	*grams*	*grams*	*calories*	*grams*	*calories 24 hours*	
A	November 25–December 2	60	44	126	1,185	12 56	2,000	0 73
B	January 16–26	63	26	148	1,078	11 1	1,746	0 76
C	December 9–24	57	22	178	1,138	10 55	1,813	0 77

n the requirement for maintenance The re-
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it will be noted that in period A in which the greatest caloric deficit exists, the dietary carbohydrate is lowest This would imply the greatest demand upon the glycogen reserve In period B and period C the only significant difference is in the dietary carbohydrate This relationship between carbohydrate in the diet and the destruction of glycogen appears to be confirmed by the trend of the fasting respiratory quotient

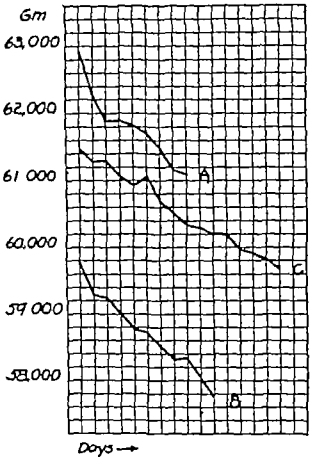

FIG 2 WEIGHT CURVES DURING THREE PERIODS OF UNDERNUTRITION

The steep initial fall in (*A*) suggests a large destruction of glycogen, whereas the relative smoothness of (*C*) suggests that little or no glycogen was destroyed The small but definitely steep initial fall in (*B*) suggests a condition intermediate between (*A*) and (*C*)

The rapid fall in weight in period A (fig 2) also indicates a considerable destruction of glycogen whereas in period C, the relatively smooth curve indicates that there was no significant destruction of glycogen The weight curve in period B suggests an intermediate condition *in regard to glycogen*

The water balance of this third period of undernutrition, when the dietary carbohydrate was relatively high and little or no glycogen was

destroyed, will be found in table 13 The metabolic data for the period are brought together in table 5 of the Appendix

The water exchange during a fourth period of undernutrition is presented next in table 14 Ten days before the beginning of this period a low calory diet consisting solely of milk and sugar was instituted and continued without change It is probably true that the

TABLE 13

Comparison between predicted and determined water balance in undernutrition

Date	Change in subject's weight	Theoretical loss	Water balance		
			Predicted	Determined	Error
1928	*grams*	*grams*	*grams*	*grams*	*grams*
December 9	−165	114	−51	−49	2
December 10	+20	114	+134	+156	22
December 11	−260	114	−146	−155	9
December 12	−120	114	−6	+6	12
December 13	+110	114	+224	+221	3
December 14	−355	114	−241	−227	14
December 15	−165	114	−51	−61	10
December 16	−170	114	−56	−60	4
December 17	−45	114	+69	+66	3
December 18	−105	114	+9	+68	59
December 19	±0	114	+114	+104	10
December 20	−230	114	−116	−128	12
December 21	−50	114	+64	+76	12
December 22	−105	114	+9	0	9
December 23	−140	114	−26	−33	7
December 24	+130		+244	+243	1
Totals			+174	+227	

Error for period 53 grams

destruction of glycogen had ceased before the period began, and that all the endogenous calories came from protein and fat Since there was a falling heat production during this long period, two metabolic mixtures were calculated

The data needed to obtain the water exchange will be found in the Appendix, tables 6 and 7 The former is for the first metabolic mixture and the latter for the second mixture

We come now to the study of water exchange in patients We have selected from our series what we consider to be an average example The subject was a girl aged fourteen years, of low mentality, and who

TABLE 14

Comparison between predicted and determined water balance in undernutrition

Date	Change in subject's weight	Theoretical loss	Water balance		
			Predicted	Determined	Error
1929	*grams*	*grams*	*grams*	*grams*	*grams*
January 26	+50	127	+177	+175	2
January 27	−115	127	+12	+33	21
January 28	−285	127	−158	−147	11
January 29	+25	127	+152	+139	13
January 30	+15	127	+142	+129	13
January 31	+35	127	+162	+175	13
February 1	−270	127	−143	−153	10
February 2	−430	127	−303	−293	10
Totals			+41	+58	
February 3	+285	97	+382	+369	13
February 4	−225	97	−128	−105	23
February 5	+65	97	+162	+149	13
February 6	−125	97	−28	−41	13
February 7	+115	97	+212	+198	14
February 8	−345	97	−248	−201	47
February 9	−150	97	−53	−55	2
February 10	−90	97	+7	−4	11
February 11	−35	97	+62	+48	14
February 12	−350	97	−253	−215	38
February 13	+20	97	+117	+101	16
February 14	−5	97	+92	+75	17
February 15	−310	97	−213	−176	37
Totals			+108	+143	
Grand Totals			+149	+201	

Error for period 52 grams

had an endocrine disturbance that had caused gigantism and precocious sexual development Her basal metabolic rate was about 25 per cent below normal She did not cooperate well with us She

was fed a mixed diet of the type described on page 163, and the water content of the food was accordingly obtained by means of the duplicate diet as described on page 163 The duplicate diet was analysed for nitrogen but not for fat or carbohydrate The food table values were used for the latter two The urine solids were obtained by dessication in a partial vacuum over sulphuric acid We found this method much less satisfactory than the procedure of Shackell (1)

The subject was allowed to be out of bed in a wheel chair several hours daily, but was not permitted to leave the room unless she was to be brought to the laboratory

When the period was over it was found that the daily record of the insensible loss was unsatisfactory since the heat production obtained from it was repeatedly less than the basal metabolic rate Upon looking back we recalled that the patient often sat in the wheel chair with bare legs in a room that, at times, was distinctly cool The small insensible loss was apparently caused by chilling the lower extremities

In order to compensate for this error we proceeded as follows A few weeks after the period just described had ended, the patient was strictly confined to bed under continuous guard Bathing was ommitted Under these conditions the total heat production for three consecutive days was 1900, 1930, and 1930 calories A number of determinations of the basal metabolic rate, preceding and following this special interval of three days, gave an average of 1506 calories The total calories when the patient was continuously confined to bed were accordingly 27 per cent more than the basal calories During the earlier period, when the insensible loss was irregular, twenty-one determinations of the basal metabolic rate gave an average of 1604 calories for 24 hours If the total calories at this time had been 27 per cent greater, they would have been 2037 But since the patient had been more active during those days we inferred that 100 calories should be added for such factors This gave us the final value of 2137 as the total twenty-four hourly heat production

Before presenting the water balances for the long period when 2137 calories was assumed to be the average heat production, it is desirable to see what results were obtained during the special three day period when the heat production was so uniform (See table 15 and Appendix, table 8) The large error of the second day was, as usual,

on a day when the patient had a very large stool The considerable errors on the other two days are largely attributable to the complicated diet

The water balances of the long period when the heat production was estimated to be 2137 calories for each twenty four hours, are presented in table 16 (The data will be found in table 9 of the Appendix)

In spite of the greater likelihood of larger errors for the reasons given above, the results are fairly satisfactory From February 25th to March 12th the patient should have lost 2996 grams of weight,

TABLE 15

Water balance in a patient confined to bed but receiving a complicated diet

Date	Change in subject's weight	Theoretical gain	Water balance		
			Predicted	Determined	Error
1918	*grams*	*grams*	*grams*	*grams*	*grams*
April 24	−157	7	−164	−134	30
April 25	−565	7	−572	−517	55
April 26	+129	7	+122	+100	22
Totals			−614	−551	
Error for period 63 grams					

but her weight fell only 10 grams during these sixteen days The predicted retention of water was 2886 grams and the data showed a retention of 2672 grams Accordingly, in spite of the complicated diet and the doubt regarding the figure obtained for heat production, the determined retention of water was only 7 per cent less than the prediction

Following the large retention of water there was an excessive output of water During the nine days from March 12 to March 21 the patient should have lost 1629 grams Since her weight fell 3995 grams, the difference, 2366 grams, was the predicted water loss The determined loss was 2266 grams In this case the determined loss was only 4 per cent less than the prediction

TABLE 16

Water balances when complicated diet is fed and subject is up in a chair during the day

Date	Change in subject's weight	Theoretical loss	Water balance		
			Predicted	Determined	Error
1928	*grams*	*grams*	*grams*	*grams*	*grams*
February 25	0	181	+181	+157	24
February 26	−85	181	+96	+66	30
February 27	−480	181	−299	−249	50
February 28	+300	181	+481	+448	33
February 29	+280	181	+461	+428	33
March 1	−350	181	−169	−144	25
March 2	−230	181	−49	−39	10
March 3	−110	181	+71	+42	29
March 4	+500	181	+681	+650	31
March 5	−290	181	−109	−48	61
March 6	−110	181	+71	+44	27
March 7	+260	181	+441	+396	45
March 8	−360	181	−179	−210	31
March 9	+170	181	+351	+338	13
March 10	−225	181	−44	−79	35
March 11	+720	181	+901	+872	29
Totals			+2,886	+2,672	
March 12	−665	181	−484	−411	73
March 13	−90	181	+91	+71	20
March 14	−640	181	−459	−434	25
March 15	−300	181	−119	−107	12
March 16	−700	181	−519	−486	33
March 17	−195	181	−14	−48	34
March 18	−875	181	−694	−673	21
March 19	−150	181	+31	+13	18
March 20	−380	181	−199	−191	7
Totals			−2,366	−2,266	
Grand Totals			+520	+406	

Error for period 114 grams

V

There remains now the discussion of the degree of accuracy of the water balance obtained by the above methods We have dealt

with this question by comparing the predicted balance with the determined balance This implies that the prediction is absolutely correct But the information at hand does not warrant such an assumption to its full extent, since the predicted balance is derived from the

TABLE 17

Error in determination of water balance

Period number	Date	Daily error			Error for period per day	Notes
		Maximal	Minimal	Average		
		grams	grams	grams	grams	
1	January 26–February 15	47	2	17	2 5	Diet completely analysed Under nutrition No destruction of glycogen
2	December 9–24	57	2	12	3 3	Diet completely analysed Under nutrition Little or no destruction of glycogen
3	January 16–25	21	0	9	1 9	Diet completely analysed. Under nutrition. Moderate destruction of glycogen
4	November 25–December 2	37	4	12	5 7	Diet completely analysed Under nutrition Much glycogen destroyed
5	December 3–8	28	8	16	7 8	Diet completely analysed. Overnu trition Much glycogen stored
6	November 13–23	53	3	21	9 7	Diet completely analysed Overnu trition No data regarding glycogen
7	January 11–15	40	2	11	4 8	Diet completely analysed. Overnu trition. No data regarding gly cogen
8	April 24–26	55	22	36	21 0	Only nitrogen of diet determined. Duplicate diet used. Overnutri tion. Period only three days
9	February 25–March 20	73	7	30	4 6	Only nitrogen of diet determined Duplicate diet used. Undernutri tion. Small destruction of gly cogen

metabolic mixture and it usually is not possible to avoid small inaccuracies in the latter Accordingly the error, as the term is used in table 17, is not a final measure of the method, but is an approximation, approaching nearest to the truth when the statement of the metabolic mixture is most nearly correct

In period 1 of table 17, the conditions were most suitable for obtaining a satisfactory statement of the materials burned The values for period 1 may, therefore, be accepted as the probable error of the method

The conditions for period 2 are only slightly different from those of period 1, so that the error is nearly the same

It will be seen that the average error is only about 15 grams per day, but that a mistake of 50 grams may occur on any single day Since the water that the subject had to deal with from day to day was about 2100 grams, the average error made in accounting for it was less than 1 per cent, and, what is more important, the maximal error was less than 3 per cent

Interestingly the errors for periods 3 and 4, when the metabolic mixture cannot be correct because it does not include the glycogen that was destroyed, are no greater Likewise, in the three periods of overnutrition, periods 5, 6 and 7 in the table, when the same doubt exists regarding glycogen, the error is of only slightly greater magnitude than in period 1

The two periods 8 and 9, when the conditions were not so simple nor so satisfactory, gave results that are better than anticipated

The last column of table 17 deals with the error in water balance for whole periods, expressed in 24 hourly amounts This is not the same as the average error, since the daily differences tend to counteract each each other and so reduce the discrepancy The error in determining the water balance for the period was always less than 0 5 per cent of the water to be dealt with, except in period 8 where the period is too short to be of much value in this regard

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TABLE 3

Normal Subject Undernutrition November 25–December 2, 1928

Date	Weight of subject 8 40 a m.	Water	Milk		Bread		Butter*	Urine			Stool		Insensible loss	Heat production
			Total	Water	Total	Water		Total	Solids	N	Total	Solids		
	grams	*grams*	*grams*	*per cent*	*grams*	*per cent*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*calories*
November 25	62,935	310	1,502	88 8	102	38 2	15	1,216	42 8	10 8	140	20	1,248	2,085
November 26	62,260	378	1,484	88 7	100	37 9	16	1,157	45 3	12 2	0		1,180	2,000
November 27	61,900	587	1,498	88 5	100	41 3	15	874	45 0	12 7	0		1,331	2,190
November 28	61,895	564	1,502	88 4	100	39 9	16	987	43 4	12 8	0		1,275	2,115
November 29	61,815	479	1,500	88 4	100	40 3	15	803	42 6	12 8	205	46	1,206	2,035
November 30	61,695	715	1,501	88 4	101	39 7	13	1,436	44 4	11 5	102	14	1,022	1,800
December 1	61,465	819	1,500	88 7	101	40 9	16	1,684	43 2	12 2	0		1,027	1,800
December 2	61,190	547	1,501	88 3	100	40 5	16	1,004	42 0	11 9	101	27	1,153	1,965
December 3	61,095													

Diet Protein 60 grams, fat 44 grams, carbohydrate 126 grams

Stool N Average 0 45 gram per day

Metabolic mixture Protein 79 grams, fat 131 grams, carbohydrate 126 grams

* Two grams daily was allowed for the water contained in the butter

TABLE 4

Normal subject Undernutrition January 16–25 1929

Date	Weight of subject 8 30 a.m.	Water	Milk		Sugar	Urine			Stool		Insensible loss	Heat production
			Total	Water		Total	Solids	N	Total	Solids		
	grams	*grams*	*grams*	*per cent*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*calories*
January 16	59,785	290	1 999	89 5	45	1 585	42 8	10 24	187	33	1 087	1 880
January 17	59 260	234	2 000	89 5	44	1 176	39 1	10 01	131	18	995	1,760
January 18	59,235	202	2,001	89 6	44	1 382	38 7	10 79	107	15	993	1 760
January 19	59,000	143	2 000	89 7	46	1 301	36 7	10 14	124	15	998	1 760
January 20	58 765	474	2 001	89 9	45	1 557	41 0	11 24	0	0	992	1 745
January 21	58 735	197	2 000	89 7	45	1,340	37 9	10 48	162	27	974	1 730
January 22	58,500	103	2,001	89 6	46	1 270	37 1	9 99	119	17	935	1,680
January 23	58,325	173	1 999	89 7	45	1 163	38 4	10 37	0	0	1 008	1,760
January 24	58 370	310	2,001	89 7	45	1 650	39 3	10 72	159	28	877	1,610
January 25	58,040	223	1,998	89 7	46	1 514	39 3	11 06	0	0	1,003	1 760
January 26	57 790											

Diet Protein 63 grams fat 26 grams carbohydrate 148 grams.

Stool N Average per day 0 6 gram.

Metabolic mixture Protein 69 grams, fat 24 grams, carbohydrate 148 grams.

TABLE 5

Normal subject Undernutrition December 9–25, 1928

Date	Weight of subject 8 40 a.m.	Water	Milk		Bread		Butter	Sugar	Urine			Stool		Insensible loss	Heat production
			Total	Water	Total	Water			Total	Solids	N	Total	Solids		
1928	*grams*	*grams*	*grams*	*per cent*	*grams*	*per cent*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*calories*
December 9	61,455	187	1,397	90 5	130	40 6	11	40	852	37 6	9 49	0	0	1,077	1,870
December 10	61,290	761	1,400	90 0	131	41 0	11	40	1,146	37 1	10 25	90	27	1,086	1,880
December 11	61,310	502	1,399	89 9	129	37 7	11	40	1,202	36 5	9 82	0	0	1,138	1,930
December 12	61,050	353	1,399	90 0	130	38 8	10	40	913	38 0	10 47	53	19	1,087	1,880
December 13	60,930	673	1,403	90 3	130	39 0	10	40	1,150	36 4	10 38	0	0	995	1,760
December 14	61,040	316	1,402	90 1	130	41 0	10	40	1,208	37 4	10 65	51	17	994	1,760
December 15	60,689	366	1,404	90 1	130	39 3	10	40	1,176	34 4	9 09	0	0	939	1,690
December 16	60,520	450	1,403	89 9	130	40 9	10	40	1,229	37 6	10 58	0	0	973	1,730
December 17	60,350	558	1,400	90 1	129	39 3	10	40	1,212	37 7	10 44	0	0	970	1,730
December 18	60,305	704	1,399	90 0	130	41 5	10	40	957	35 1	9 90	321	62	1,107	1,900
December 19	60,200	417	1,396	90 1	130	37 0	10	40	1,016	34 4	9 66	0	0	977	1,740
December 20	60,200	194	1,401	90 0	129	39 8	10	40	906	30 9	10 32	0	0	1,098	1,890
December 21	59,970	335	1,399	89 8	130	37 8	9	39	789	32 8	10 45	110	28	1,063	1,850
December 22	59,920	448	1,400	90 1	129	38 6	10	40	855	32 9	10 70	0	0	1,276	2,115
December 23	59,815	67	1,403	90 0	130	40 4	11	41	718	37 7	9 85	0	0	1,074	1,860
December 24	59,675	255	1,398	90 6	128	36 7	10	40	644	37 0	9 94	0	0	1,058	1,840
December 25	59,805														

Diet Protein 57 grams, fat 22 grams, carbohydrate 178 grams

Stool N Average per day 0 43 gram.

Metabolic mixture Protein 66 grams, fat 93 grams, carbohydrate 178

TABLE 6

Normal Subject Undernutrition January 26–February 2

Date	Weight of subject 8.40 a.m.	Water	Milk		Urine			Stool			Insensible loss	Heat production
			Total	Water	Total	Solids	N	Total	Solids	N†		
	grams	*grams*	*grams*	*per cent*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*calories*
January 26	57 790	75	1 997	90 1	1 108	39 2	11 07	0		0 6	958	1 715
January 27	57,840	283	2 000	89 7	1,350	41 2	11 21	113	29	0 6	979	1 730
January 28	57 725	119	2 000	89 6	1 156	37 9	11 25	147	25	0 6	1 145	1 950
January 29	57 440	68	2 000	89 7	959	38 2	10 95	0		0 6	1 128	1,930
January 30	57 465	159	2 015	89 7	1 206	39 1	11 73	0		0 6	998	1 760
January 31	57 480	193	2,023	89 7	1,111	38 5	11 33	105	27	0 6	1 010	1 780
February 1	57 515	147	1 997	89 7	1 422	40 2	11 38	0		0 6	1 037	1 815
February 2	57 245	0	2 001	89 7	1 334	39 8	10 66	85	20	0 6	1 057	1 840

Diet Protein 63 grams (N × 6 25) fat 26 grams (Babcock) carbohydrate 148 grams (by difference—sucrose 45 grams)

Metabolic mixture Protein 74 grams fat 103 grams carbohydrate 148 grams

* To obtain total weight of diet add 45 grams for sucrose

† The stool from January 26 to February 15 was mixed and analysed in duplicate for N The value obtained was apportioned per day

TABLE 5

Normal subject Undernutrition December 9–25, 1928

Date	Weight of subject 8 40 a.m.	Water	Milk		Bread		Butter	Sugar	Urine			Stool		Insensible loss	Heat production
			Total	Water	Total	Water			Total	Solids	N	Total	Solids		
1928	*grams*	*grams*	*grams*	*per cent*	*grams*	*per cent*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*calories*
December 9	61,455	187	1,397	90 5	130	40 6	11	40	852	37 6	9 49	0	0	1,077	1,870
December 10	61,290	761	1,400	90 0	131	41 0	11	40	1,146	37 1	10 25	90	27	1,086	1,880
December 11	61,310	502	1,399	89 9	129	37 7	11	40	1,202	36 5	9 82	0	0	1,138	1,930
December 12	61,050	353	1,399	90 0	130	38 8	10	40	913	38 0	10 47	53	19	1,087	1,880
December 13	60,930	673	1,403	90 3	130	39 0	10	40	1,150	36 4	10 38	0	0	995	1,760
December 14	61,040	316	1,402	90 1	130	41 0	10	40	1,208	37 4	10 65	51	17	994	1,760
December 15	60,689	366	1,404	90 1	130	39 3	10	40	1,176	34 4	9 09	0	0	939	1,690
December 16	60,520	450	1,403	89 9	130	40 9	10	40	1,229	37 6	10 58	0	0	973	1,730
December 17	60,350	558	1,400	90 1	129	39 3	10	40	1,212	37 7	10 44	0	0	970	1,730
December 18	60,305	704	1,399	90 0	130	41 5	10	40	957	35 1	9 90	321	62	1,107	1,900
December 19	60,200	417	1,396	90 1	130	37 0	10	40	1,016	34 4	9 66	0	0	977	1,740
December 20	60,200	194	1,401	90 0	129	39 8	10	40	906	30 9	10 32	0	0	1,098	1,890
December 21	59,970	335	1,399	89 8	130	37 8	9	39	789	32 8	10 45	110	28	1,063	1,850
December 22	59,920	448	1,400	90 1	129	38 6	10	40	855	32 9	10 70	0	0	1,276	2,115
December 23	59,815	67	1,403	90 0	130	40 4	11	41	718	37 7	9 85	0	0	1,074	1,860
December 24	59,675	255	1,398	90 6	128	36 7	10	40	644	37 0	9 94	0	0	1,058	1,840
December 25	59,805														

Diet Protein 57 grams, fat 22 grams, carbohydrate 178 grams

Stool N Average per day 0 43 gram

Metabolic mixture Protein 66 grams, fat 93 grams, carbohydrate 178

TABLE 6

Normal Subject. Undernutrition. January 26–February 2

Date	Weight of subject 8.40 a.m.	Water	Milk*		Urine			Stool			Insensible loss	Heat production
			Total	Water	Total	Solids	N	Total	Solids	Nt		
	gram	*grams*	*grams*	*per cent*	*c.c.s*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*calories*
January 26	57 790	75	1 997	90 1	1,108	39 2	11 07	0		0 6	958	1 715
January 27	57 840	283	2 000	89 7	1 350	41 2	11 21	113	29	0 6	979	1 730
January 28	57 725	119	2 000	89 6	1 156	37 9	11 25	147	25	0 6	1 145	1,950
January 29	57 440	68	2 000	89 7	959	38 2	10 95	0		0 6	1,128	1 930
January 30	57 465	159	2 015	89 7	1 206	39 1	11 73	0		0 6	998	1 760
January 31	57 480	193	2 023	89 7	1 111	38 5	11 33	105	27	0 6	1 010	1 780
February 1	57 515	147	1 997	89 7	1 122	40 2	11 38	0		0 6	1 037	1 815
February 2	57 245	0	2 011	89 7	1,331	39 8	10 66	85	20	0 6	1 057	1 840

[illegible] grams (N × 6.25) [illegible] 24 grams (Hathcock); carbohydrate 148 grams (by difference—sucrose 45 grams)

[illegible] 45 gm. [illegible] 181 grams; carbohydrate 118 grams

[illegible] grams for sucrose

[illegible] was milked and analysed in duplicate for N. The value obtained was apportioned per day

TABLE 7

Normal subject Undernutrition February 3–15, 1929

Date	Weight of subject 8 40 a m.	Water	Milk		Urine	Stool		
			Total	Water		Total	Solids	N
1929	*grams*	*grams*	*grams*	*per cent*	*grams*	*grams*	*grams*	*grams*
February 3	56,815	166	2,000	89 7	905	0		0 6
February 4	57,100	88	2,000	89 7	1,236	188	37	0 6
February 5	56,875	74	2,002	89 7	985	0		0 6
February 6	56,940	121	2,000	89 7	1,340	0		0 6
February 7	56,815	249	2,000	89 7	1,257	0		0 6
February 8	56,930	200	2,001	89 7	1,360	300	62	0 6
February 9	56,585	134	1,999	89 7	1,303	60	10	0 6
February 10	56,435	430	2,001	89 7	1,696	0		0 6
February 11	56,345	73	2,000	89 7	1,274	0		0 6
February 12	56,310	86	2,001	89 7	1,180	361	53	0 6
February 13	55,960	0	2,001	89 7	1,132	0		0 6
February 14	55,980	117	1,999	89 7	1,326	0		0 6
February 15	55,975	43	1,990	89 7	1,106	288	44	0 6
February 16	55,670							

Diet and stool N The same as in table 6

Metabolic mixture Protein 69 grams, fat 91 grams, carbohydrate 148 grams

TABLE 8

Overnutrition with mixed diet April 24–26, 1928

Date	Weight of subject 8 25 a.m.	Water	Patient's diet	Duplicate diet		Urine			Stool		Insensible loss	Heat production
				Total	Dry	Total	Solids	N	Total	Solids		
1928	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*calories*
April 24	90,927	1 202	1 568	1,593	420	1 652	56	12 12	179	38	1 096	1 900
April 25	90 770	1 235	1 527	1,503	381	1 579	55	12 19	620	73	1 128	1,930
April 26	90 205	1,327	1 466	1 445	384	1 540	54	12 65	0		1 124	1 930
April 27	90 334											

Diet (food tables) Protein 85 grams, fat 100 grams carbohydrate 186 grams

N in 85 + 6.25 = 13 6 grams. N out, 12.3 (urine) + 10 per cent for stool = 13 5 grams.

Metabolic mixture Protein 85 grams, fat 93 grams, carbohydrate 186 grams.

Undernutrition with mixed diet February 25 to March 20, 1928

Date	Weight of subject 8 45 a.m	Water	Patient's diet	Duplicate diet		Urine			Stool		Insensible loss
				Total	Dry	Total	Solids	N	Total	Solids	
1928	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*
February 25	94,200	797	1,056	1,052	192	1,111	32 7	9 97	0		742
February 26	94,200	928	1,050	1,034	196	1,304	42 2	13 88	0		759
February 27	94,115	1,255	1,050	1,055	193	905	23 8	7 62	467	75	1,413
February 28	93,635	1,252	1,035	1,024	188	1,077	26 9	9 43	0		910
February 29	93,935	1,343	984	974	200	1,354	38 0	11 47	0		693
March 1	94,215	1,042	1,089	1,085	200	1,131	26 8	7 60	401	63	949
March 2	93,865	788	1,024	1,034	181	1,177	41 6	13 02	0		865
March 3	93,635	1,891	965	957	200	2 086	40 4	11 88	0		880
March 4	93,525	1,366	1,023	1,019	201	1,148	35 1	11 36	0		741
March 5	94,025	1,152	1,066	1,064	197	1,220	36 3	10 43	432	85	856
March 6	93,735	1,036	1,026	1 018	199	1,448	40 6	11 18	0		724
March 7	93,625	1,611	1,061	1,052	207	1,293	31 6	9 70	0		1,119
March 8	93,885	1,062	1,062	1,056		1,138	18 7?	6 08	0		1,346
March 9	93,525	1,435	1,038	1,036	187	1,255	35 7	10 05	0		1,048
March 10	93,695	754	976	967	201	1,096	36 4	10 07	0		859
March 11	93,470	1,632	1,005	1,004	211	854	44 1	10 43	0		1 063
March 12	94,190	1,151	1,087	1,072	205	1,466	38 5	10 66	434	115	1,003
March 13	93,525	1,306	986	992	202	1,602	37 0	9 38	0		780
March 14	93,435	1,101	1,033	1,025	192	1,708	41 8	11 21	199	44	867
March 15	92,795	1,735	971	957	192	1,305	26 4	6 60	390	53	1,311
March 16	92,495	1,519	1 065	1,047	179	1,815	38 3	9 36	554	53	915
March 17	91,795	1,900	1,013	1,012	223	1,937	50 5	11 21	0		1,171
March 18	91,600	1,281	969	961	189	1,798	37 7	10 08	339	41	988
March 19	90,725	1,316	1,089	1 087	215	1,440	37 8	11 07	202	21	913
March 20	90,575	1,409	1,030	1,023	201	1,268	35 5	10 25	385	41	1,166
March 21	90,195										

Diet Protein 64 5 grams (N × 6 25), fat 40 grams (food table), carbohydrate 74 grams (food table)
Stool N Average daily 1 32 grams
Metabolic mixture Protein 73 grams, fat 172 grams, carbohydrate 74 grams

THE NATURE OF OBESITY[1,2]

L. H. NEWBURGH AND MARGARET WOODWELL JOHNSTON

(From the Department of Internal Medicine, Medical School University of Michigan, Ann Arbor)

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The medical profession in general, believes that there are two kinds of obese persons—those who have become fat because they overeat or under-exercise, and those composing a second group whose adiposity is not closely related to diet, but is caused by an endocrine or constitutional abnormality

The first apparently scientific support of the hypothesis that obesity was often of endogenous origin, came with the finding that some obese persons had an abnormally low basal metabolic rate, on the basis of body weight When, however, it was shown that the expenditure of energy is proportional to the surface area and not the weight, it was found that most such persons have a normal basal metabolic rate However, it is true that there remains a small group of fat people whose basal rate is definitely low

Later writers maintained that a common cause of endogenous obesity was to be found in a lessened specific dynamic response to food. But the increase in metabolic rate caused by food is relatively small, so that a method possessed of a high degree of accuracy is needed in order to deal quantitatively with this phenomenon Our prolonged study of this question has convinced us that the inherent error in the method to date, when it is applied to the human subject, is such that it precludes the possibility of making quantitative statements regarding the specific dynamic response to food in man

Other writers have attributed endogenous obesity to a constitutional anomaly of the cells which somehow lowers the rate of intracellular oxidations

[1] Address delivered before the American College of Physicians

[2] Aided by a grant from The Fellowship Corporation

But even if there were a group of obese people who possessed all these metabolic faults, we would still be without an adequate explanation for the occurrence of the adiposity For 1—many persons of normal stature show abnormally low metabolic rates For example, the average of a number of determinations in a middle aged woman under our care, who weighs 130 pounds, is 40 per cent below normal A tall,

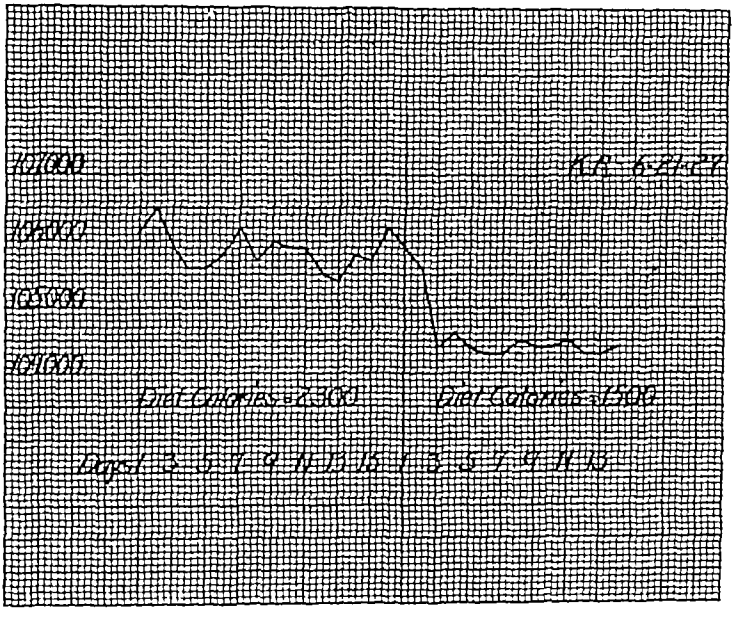

FIG 1 RESPONSE OF AN OBESE SUBJECT TO UNDERNUTRITION

The diet in the first period is at the maintenance level In the second period, no weight is lost for eleven consecutive days even though the diet is deficient to the extent of 800 calories daily

slight young man regularly has a basal metabolic rate which is 25 per cent below normal Myxedematous patients may lose weight 2—The same writers who attribute endogenous obesity to a lessened specific response to food, describe other forms of pituitary disease characterized by the small increase in metabolic rate due to food, but without adiposity 3—On the other hand the well known fall in basal metabolic rate caused by undernutrition in the normal subject, often fails to occur in the type of obesity under consideration (1), and further, it has

recently been established that the obese subject uses more energy to perform a given piece of work than does the normal person (2)

These considerations lead to the conclusion that the fundamental cause of endogenous obesity is not to be found in some type of metabolic abberation, but rather, that these individuals, in common with all obese persons, are the victims of a perverted appetite In normal people there is a mechanism that maintains an accurate balance between the outgo and the income of energy All obese persons are, alike in one fundamental respect,—they literally overeat

Regardless of any theoretical consideration, it is a fact that obese persons may fail to lose weight for a number of days when they are being undernourished We have repeatedly recorded this striking phenomenon For example, figure 1 is a portion of the weight record of a girl who weighed 231 lbs During the first period she received her maintenance calories In the second period, when she was deriving 800 calories a day from her body, she lost no weight for eleven consecutive days It is this startling fact that is behind the search for some hidden metabolic fault inherent in these subjects We likewise, have centered our attention upon this feature but have attempted its explanation with a new point of view In the past it has been customary to determine the basal metabolic rate and then guess how many additional calories were used during the twenty-four hours When a diet containing less energy than the subject was thought to be using, was fed, the extra calories used by the subject but not contained in the diet, were assumed to arise from the oxidation of body fat, and the number of grams of fat required to make up the caloric deficit of the diet, formed the basis for the prediction of the amount of weight that the subject should lose

We have considered such methods too inaccurate Above all, it seemed necessary to have a means of getting an actual quantitative determination of the total outgoing calories Fortunately recent studies by Benedict and Root (3) have made such a method available for the basal state, and we have been able to adapt it to our special problem

It was understood many hundred years ago that there was a constant exhalation of invisible material from the body Sanctorius (1614) made many observations to determine the amount of this

"insensible perspiration" The subject has been studied sporadically ever since, but Francis G Benedict and his collaborators were the first to point out that there is a quantitative relationship between the amount of weight lost by the body insensibly and the metabolic rate They found that when a subject in the basal state is suspended from one arm of a delicate balance, he loses weight at an even rate For example, a loss of 30 grams per hour corresponds to a metabolic rate of 1405 calories per twenty-four hours We have been able to confirm this observation for the basal state, and further have found that the

TABLE 1

Determination of total calories for 24 hours

I		II	
	grams		*grams*
First body weight	62,260	Second body weight	61,900
Weight of food	1,599	Weight of urine	1,157
Weight of water	378	Weight of stool	0,000
	64,237		63,057
	63,057		
	1,180		

1,180 grams is insensible loss for 24 hours

$\frac{1,180}{24} = 49.2$ grams insensible loss per hour

or

2,000 calories for the 24-hour period

same principle may be applied in the determination of the total number of calories lost in twenty-four hours If a subject is weighed at the beginning and end of a twenty-four hour period and if the weight of food and drink are added to the first body weight, and the weight of the urine and stool are added to the second body weight, the difference between the first and second sums is the insensible loss for twenty-four hours From this figure the loss of weight per hour is obtained and finally, by means of Benedict's prediction table, the total calories for the period [3]

[3] We have discussed the sources of error and indicated the high degree of accuracy obtainable by this method in another publication (4)

For the sake of clarity the figures used to determine the total calories for a single twenty-four hour period are reproduced in table 1

Of equal importance with a method for determining the energy used by an individual, is an acurate knowedge of the response by a normal person to undernutrition May he perhaps also fail to lose weight in accord with the expectation?

Fortunately we have been able to obtain this information by means of one of the laboratory staff who acted as the subject His coöperation was perfect at all times and his absolute honesty is beyond question [4] Briefly, the man remained in bed, except when he stepped from it to the adjoining scale to be weighed or to the commode, a few feet away, to void or defecate into the special receptacles provided, or to place himself on a wheel chair by means of which he was moved to the laboratory where the basal metabolic rate was determined His diet consisted solely of milk, sugar and water His intake of these materials was weighed to one tenth of a gram and a sample of the milk was analysed for water content, nitrogen, fat, ash and carbohydrate The excreta were similarly weighed and analysed We accordingly had the following data to deal with

(1) The subject's weight within 5 grams every morning at 8 40
(2) The weight of food and drink
(3) The weight of the urine and stool
(4) The precise composition of the diet
(5) The total outgoing nitrogen, total urinary solids, the amount of fat and carbohydrate in the stool

This permitted us to calculate

(1) The twenty four hourly insensible loss of weight from which we derived the total outgoing calories for each twenty four hours
(2) The calories of the diet
(3) The calories derived from the body to make up the difference between the ingoing and outgoing calories
(4) The total amount of protein burned (total N out $\times$ 6.25)
(5) The protein loss from the body by substraction of the dietary protein from total protein burned.

[4] Space will not be taken here for a complete description of this study, the details of which are published elsewhere (5)

(6) The metabolic mixture, that is, the materials oxidized each twenty-four hours This consisted of the total protein burned, plus the carbohydrate[5] of the diet, plus the amount of fat that would furnish the calories used by the subject, not contained in the protein and carbohydrate oxidized

(7) The predicted loss of weight The difference between the protein of the diet and that of the metabolic mixture and between the fat of the diet and that of the metabolic mixture, give the weight of the protein and fat lost by the body Each of these substances has water physically

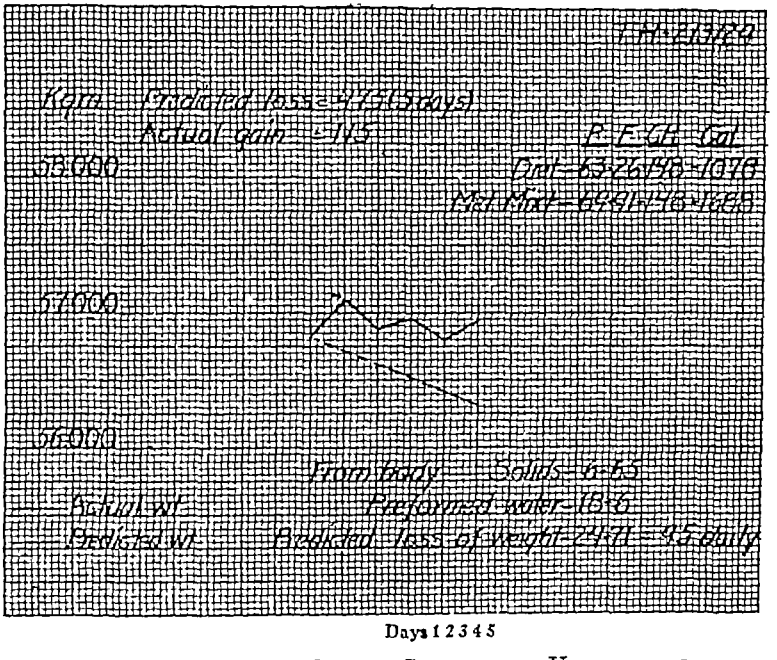

FIG 2 RESPONSE OF A NORMAL SUBJECT TO UNDERNUTRITION
He gained 115 grams in 5 days instead of losing 475 grams

attached to it which is released and free to leave the body when they are oxidized Protein is considered to hold 300 per cent and fat 10 per cent of its weight as "preformed water" The predicted loss of weight is then the sum of the weights of the protein and fat destroyed and the preformed water

In figure 2 a short portion of our study of the normal subject is represented graphically The diet consisted of protein 63 grams, fat

[5] Permissible because in undernutrition, all the carbohydrate of the diet is used

26 grams, and carbohydrate 148 grams, and contained 1078 calories The total calories used by the subject averaged 1688 for each twenty-four hour period The metabolic mixture burned to furnish that amount of energy was protein 69 grams, fat 91 grams, carbohydrate 148 grams, and the destruction of body protein and fat were consequently, 6 grams and 65 grams respectively The weight of the protein plus the water held by it (300 per cent) and of the fat and its water

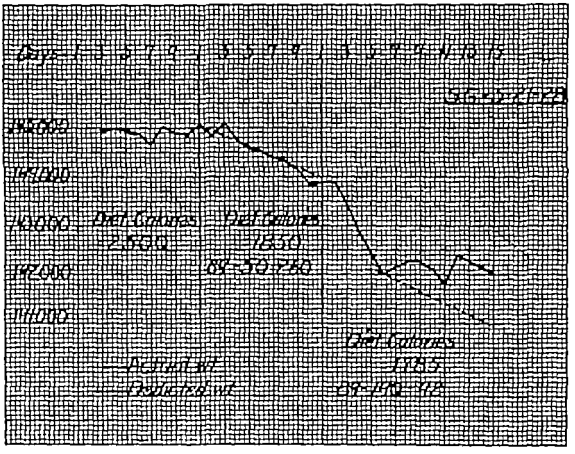

FIG 3 RESPONSE OF AN OBESE SUBJECT TO UNDERNUTRITION

The maintenance of weight in the third period is contrasted with the expected loss of weight in the second period

(10 per cent) was 95 grams The subject would accordingly be expected to lose 95 grams daily This predicted loss of weight is represented in figure 2 by the broken line His actual weight is indicated by the solid line It is evident that he gained weight for five days Since the initial weight was 56,815 grams, he should at the end of five days have weighed 56,340 grams but he did, in fact, weigh 56,930 grams, that is he had gained 115 grams and weighed 590 grams more than the prediction Here then is the production in a normal subject

of the very phenomenon whose occurrence in obese individuals had, in the minds of earlier writers, marked such persons as the victims of some endocrine or other constitutional dyscrasia

Since a normal man may gain instead of losing weight even though he takes in less energy than he uses, it is clear that this event can no longer be held to give any specific information about the nature of the obesity

As further evidence of the nonspecific character of this paradoxical conduct of the weight, figure 3 is presented The patient whose response to undernutrition is here recorded was a woman of 26 years who freely admitted that she had been overeating for a long time and that she sought our help in breaking what she herself recognized as a bad habit Except for obesity she presented no abnormalities Her basal metabolic rate was normal

Three consecutive periods are reproduced in figure 3 During the first one she received a maintenance diet The second one is the record of a simple loss of weight due to undernutrition which adheres closely to the expectation But this is abruptly followed in the third period by maintenance of weight for 9 days even though undernutrition is still in effect Here then we have in a single obese subject, first a loss of weight characteristic of (so-called) simple obesity, and shortly thereafter the failure to lose weight, that, by contrast, has been dignified as a pathognomonic sign of endogenous obesity

It is a relatively simple matter to cause either variety of weight curve If it is desired to have the subject, whether normal or obese, lose weight regularly day after day, he is fed a diet whose calorific value is less than the energy used by him, but containing an abundance of carbohydrate When the intention is to obtain a plateau in the weight curve, a diet is fed that not only yields less than the maintenance calories but is also poor in carbohydrate This restriction of the dietary carbohydrate will cause the organism to deplete its store of liver glycogen and will inevitably cause a rapid loss of weight When a balance has been reached between the exogenous and endogenous carbohydrate, the destruction of glycogen diminishes, and, at this time the subject may abruptly stop losing weight or may even gain for some days

When an individual is undernourished, the shape of the weight

curve is determined by the quality of the diet, and is in no sense dependent upon the constitutional or endocrinal state of the individual

The ability of an individual to maintain his weight when the conditions are such that a continuous loss of adipose tissue is expected, has been interpreted by some observers as evidence that such persons are endowed with a special type of metabolism which, seemingly, is not constrained to obey the law of the conservation of energy It is however, not necessary to go so far afield for an answer to what, on the sur-

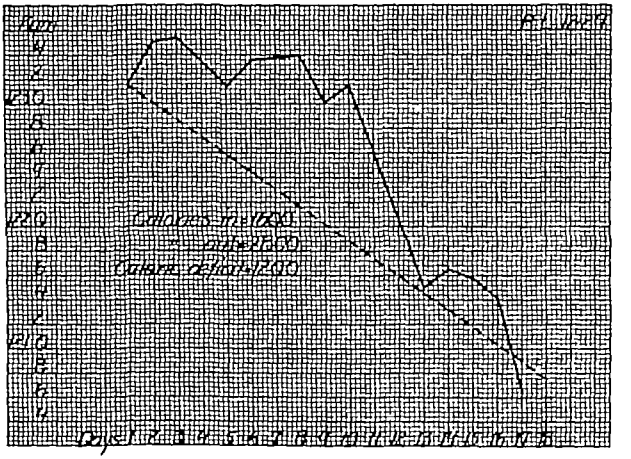

FIG 4 UNDERNUTRITION A PLATEAU IN THE WEIGHT CURVE IS FOLLOWED BY AN EXCESSIVE LOSS OF WEIGHT

face appears to be a hopelessly involved set of phenomena If the conditions that have caused a plateau in the weight curve be continued it will be observed after a few more days that an abrupt downward inclination in the curve has taken place and that the individual is now losing weight at a much more rapid rate than can be accounted for by destruction of body tissue This excessive loss of weight continues until the total loss calculated from the beginning of the plateau approximately equals the predicted loss due to the oxidation of body

tissue Figure 4 is a typical example of this phenomenon. The patient was a young woman who weighed 275 pounds when admitted to the hospital She had a basal metabolic rate of 2100 calories The diet yielded 1600 calories

This departure from the simple straight line loss of weight might be caused by alternate hydration and dehydration of the body accompanying the steady destruction of tissue in amounts that adhere closely to the prediction We have accordingly carried out a quantitative study of the water exchange in a number of obese persons and in our normal subject On one side of the equation is all the water which

TABLE 2

Determination of water lost insensibly

I		II	
	grams		*grams*
First weight	57,790	Second weight	57,840
Weight of food	2,041	Weight of urine	1,108
Weight of water	75	Weight of stool	0,000
Weight of oxygen	570	Weight of CO_2	628
	60,476		59,576

60,476
59,576
900 Water lost insensibly

becomes physically free during the period and must therefore be dealt with by the organism For convenience we have called this the "available water" On the other side is all of the water lost from the body during the period [6]

The available water is the sum of the (1) water drunk as such, (2) the water content of the food, (3) the water made by oxidizing the hydrogen of the metabolic mixture, (4) the preformed water which is water held by the body tissues and released when they are destroyed to supply energy The water that leaves the body is the sum of the (1) water of the urine, (2) water of the stool, (3) water lost insensibly from lungs and skin This last can only be determined by difference

[6] This subject is dealt with only in outline in this paper For technical and other details the reader is referred to our special publication (5)

The method is as follows To the weight of the subject at the beginning of the period is added the weight of food and drink and the weight of the oxygen added to the body for the combustion of the metabolic mixture From this sum is subtracted the sum of the weight of the subject at the end of the period, plus

TABLE 3

Water exchange

Available water		Water lost	
	grams		*grams*
Drank	75	In urine	1,069
In food	1 799	In stool	0 000
Preformed	41	Insensibly	900
By oxidation	229		1,969
	2,144		
	2,144		
	1 969		
	175	Water retained	

TABLE 4

Actual		Predicted	
Change in weight			
	grams		*grams*
First body weight.	57 790	Body protein plus preformed water	44
Second body weight	57 840	Body fat plus preformed water	85
Gain	50	Loss	129
Retention of water			
	grams		*grams*
(From analytical data)	175	Predicted loss of weight	129
		Real gain in weight	50
			179

the weights of the urine, stool and the carbon-dioxide exhaled The calculation of the weight of the insensible water from the data for a single twenty-four hour period will be found in table 2

In table 3 the calculation of the total water exchange for the same twenty-four hours is given

On this day when the subject retained 175 grams of water, the inflow and outflow of energy was such that he should have oxidized body tissues, which together with the water physically held by them, weighed 129 grams In spite of this, the body weights recorded, show a gain of 50 grams To account for this gain in terms of water, he should have retained 179 grams From our calculations were found a retention of 175 grams (table 4)

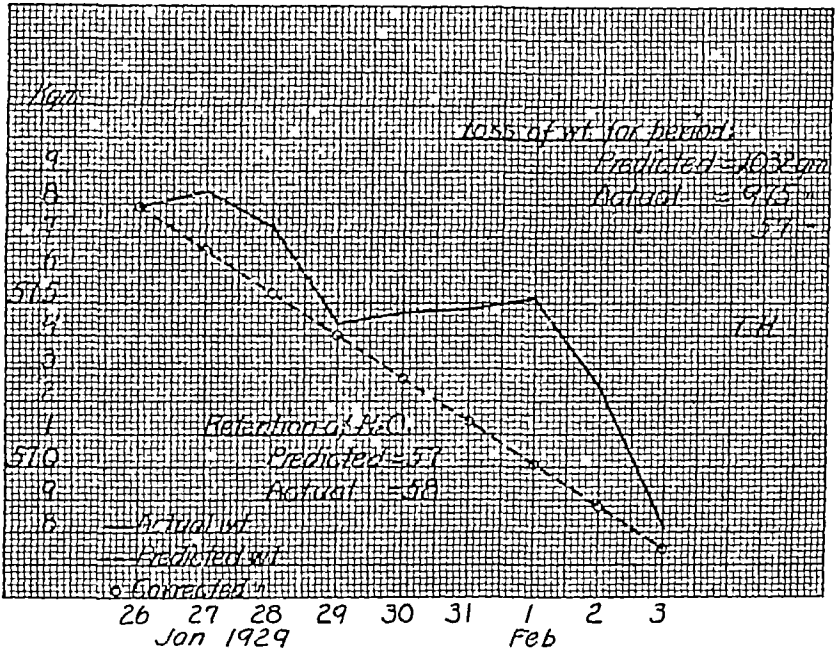

FIG 5 NORMAL SUBJECT DURING UNDERNUTRITION

When the actual daily weight is corrected by the amount of water retained or lost the resultant (indicated by circles) has the same value as the predicted weight

These studies have brought out the fact that the body weight is the combined result of two processes which may act in the same direction or be opposed to each other On the one hand there may be either an addition to the body or a loss from it of solid material, determined by the relation between ingoing and outgoing calories On the other hand, and independent of it, a retention or loss of water may occur Accordingly, when it is desired to use changes in body weight as a

measure of the amount of body tissue destroyed to make up the caloric deficit of a diet, it is necessary to correct the actual body weight by the weight of the water added to or lost from the body

We have in this manner corrected the day to day weights of a number of persons in the state of undernutrition Various types of obese persons as recorded in the literature were included, that is, an individual physically normal except for adiposity who frankly admitted years of gluttony, a feeble minded girl with an abnormally low basal metabolic rate, a girl with pituitary disease and a basal rate 30 per cent

TABLE 5

Diet (by analysis) Protein 63 Fat 26 Carbohydrate 148 Calories 1079
Calories used each 24 hours 1818
Total N out (24 hours) 11 8 grams
Metabolic mixture Protein 74, Fat 103, Carbohydrate 148

From body (daily) Protein 11, Fat 77 Water 41
Predicted loss (daily) 129 grams

Loss for period (8 days)

	grams
Predicted	1032
Actual	975
Difference	57

Retention of water

	grams
Predicted	57
Actual	58

below normal, a middle aged woman, whose weight had reached 295 pounds, following an operation upon the hypophysis eight years earlier, a young woman suffering from "Dercum's" disease, a middle aged woman, five feet two inches tall, whose weight had reached 420 pounds

We found that departures from the predicted weight were always accounted for by storage or loss of water Our data permit the conclusion that obese individuals oxidize body tissues in amounts precisely required to make up the caloric deficit of the diet

The application of this principle to the undernourished normal subject is shown in figure 5 The broken line represents the predicted loss

of weight, the solid line the actual weight, and the circles the body weight corrected each day by adding or subtracting the weight of water retained or lost during the preceding twenty-four hours The diagram

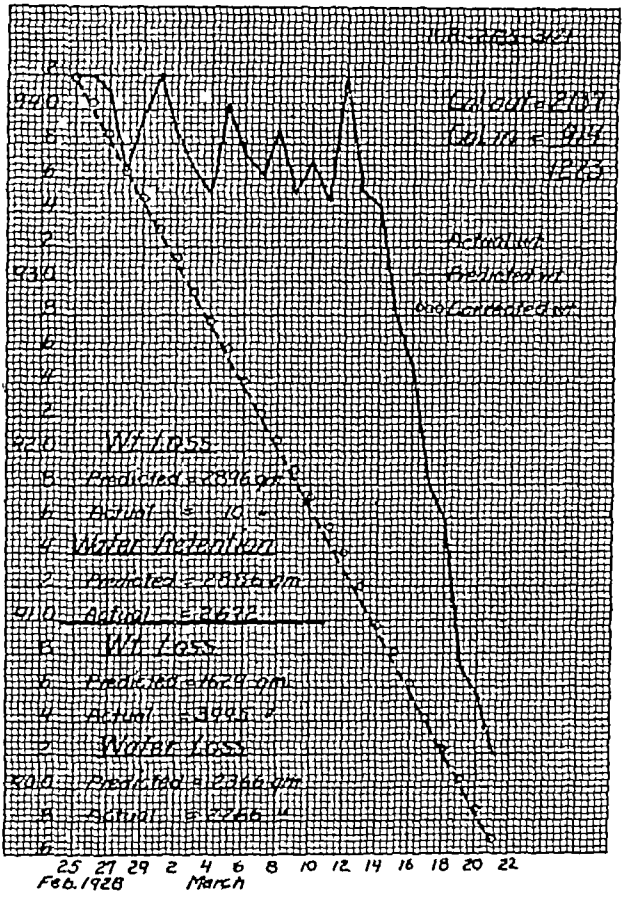

FIG 6 OBESE SUBJECT (DISEASE OF HYPOPHYSIS) DURING UNDERNUTRITION

Actual daily weight corrected for retention or loss of water The resulting figures show that the patient lost tissue in accord with the prediction

makes it clear that the weight of the normal subject may be far from the expectation, but that the difference is solely due to water

The data from which figure 5 was constructed are stated in table 5

Figure 6 shows how misleading the actual weights of an obese subject who is being undernourished may be and how the correction of such

weights for the aberrations of water cause them to correspond closely with those justified by the metabolic data (table 6)

The patient was a girl fourteen years of age who, as far back as she could remember, had been taller and fatter than the girls of her age Her progress in school had always been slow and she had repeated many of the grades Her appetite had always been excellent and she freely admitted chronic overeating She did not enjoy physical activity but preferred sitting quietly without occupation Menstruation had begun when she was ten years old and had been regular ever since

TABLE 6

Diet Protein 65, Fat 40 Carbohydrate 74 Calories 914
Total N out (daily) 11 7 grams
Calories used each 24 hours 2137
Metabolic mixture Protein 73, Fat 172 Carbohydrate 74
From body (daily) Protein 9, Fat 132, Water 40

Period A Plateau

Loss of weight		Retention of water	
	grams		*grams*
Predicted	2 896	Predicted	2,886
Actual	10	Actual	2 672

Period B Steep fall

Loss of weight		Loss of water	
	grams		*grams*
Predicted	1,629	Predicted	2 66
Actual	3,995	Actual	2 266

She was six feet one inch tall and weighed 244 pounds when admitted to the hospital Her tongue was exceptionally thick and broad There was a luxuriant growth of axillary and pubic hair and the breasts were large The basal metabolic rate was about 25 per cent below normal

CONCLUSION

Our evidence leads to the generalization that obesity is always caused by an inflow of energy that is greater than the outflow

Obese persons may be divided into two groups The first group is by far the larger and in them the laying on of fat is the outcome of a

perverted habit The normal person unconsciously provides his body with stores of energy that accurately replace his energy losses He possesses a mechanism that notifies him when he has eaten enough At that point his desire for food ceases abruptly The obese members of the first group, through long training, have come to require stimuli of greater intensity before they feel satisfied, or else they deliberately disregard the warning in order to continue a little longer the pleasures that come with eating Some persons have succeeded in dulling the acuity of the sensations concerned by following the example of their overfed elders or, in fact, have been deliberately trained to overeat by their parents Such persons are said to be suffering from hereditary obesity—a palpable fallacy In other persons the combination of weak will and a pleasure seeking outlook upon life, lays the background for the condition The mental make-up of these people resembles that of the chronic alcoholics

In the second group are those persons who in the past have accurately met their energy requirements by taking in just the right amount of food, but who have entered a new state in which the utilization of energy is less than formerly The established habit of providing the body with a fixed number of calories continues even though the requirements have fallen The lessened outflow of energy has many causes They may be thought of under two headings (1) The basal metabolic rate remains normal but the total calories used are lessened because of advancing years, the acquisition of worldly goods, change of occupation, etc (2) The basal rate becomes abnormally low as the result of myxedma or other diseases of the endocrine glands In these persons there is also a diminution of general activity However, adiposity does not invariably develop in this second class It occurs commonly under these circumstances because the firmly established habit that for many years had supplied the ideal amount of energy does not change easily

In conclusion we wish to commit ourselves to the statement that obesity is never directly caused by abnormal metabolism but that it is always due to food habits not adjusted to the metabolic requirement—either the ingestion of more food than is normally needed or the failure to reduce the intake in response to a lowered requirement

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A CASE OF OSTEITIS FIBROSA CYSTICA (OSTEOMALACIA?) WITH EVIDENCE OF HYPERACTIVITY OF THE PARATHYROID BODIES METABOLIC STUDY I[1]

By R. R. HANNON E SHORR, W S McCLELLAN and E F DuBOIS

(From the Russell Sage Institute of Pathology in affiliation with the Second Medical (Cornell) Division of Bellevue Hospital, New York)

(Received for publication July 15 1929)

The history, general discussion and outstanding features of osteitis fibrosa cystica may be found in any system of medicine (1, 2) The mineral metabolism of osteitis fibrosa cystica and related diseases, such as osteomalacia and rickets, where there is a disturbance in the physiology of inorganic salt deposit has received much attention recently

In January 1926, a patient showing evidence of marked bone absorption with little replacement of calcium was admitted to Bellevue Hospital Extensive studies of this rare condition were made in the metabolism wards of the Russell Sage Institute of Pathology, New York, and of the Massachusetts General Hospital, Boston This article will present a clinical résumé of the case with the various findings of the first period of observation

CASE REPORT

History The patient Charles M , age 30, was admitted to Bellevue Hospital January 15, 1926 He was a master mariner in the merchant marine and in 1918 was navigating officer of a transport. He was at that time in fine physical condition an active athlete 6 feet 1 inch tall His habits were good, his medical history uneventful and during his war service he was subjected at times to the nervous strain of navigating in the war zone There were periods when his diet was low in calcium as he had almost no milk eggs or green vegetables In November 1918 when 22 years old, he slipped and felt a sharp severe pain in his right loin which lasted one week Three months later pains were felt in the legs and hips, which became more severe, and extended upward to the lumbar spine

[1] Presented in abstract before the Interurban Clinical Club, New York, April, 1927

About July 1919, his fellow officers noted that he was growing shorter and becoming pigeon breasted His neck shortened and thickened so that he had to wear larger collars About the same time he noticed that he sometimes passed thick white gravel at the end of urination and that the urine was very cloudy The passing of the gravel caused severe pain The occurrence of gravel continued until 1925 His right patellar ligament was ruptured in 1920 He stumbled easily because he had difficulty in coördinating muscular movements Pains in the heels, legs, and back were caused by the jars of walking, or coming down stairs He became so weak that he could hardly climb stairs Despite these disabilities he remained at sea until 1922 when he was obliged to return to New York for treatment on account of abdominal pain and vomiting He was then 5 feet 8½ inches tall He was treated for one year for arthritis with no improvement

In October 1923, he stumbled, fell against a chair, and broke both bones of the left forearm A roentgenogram taken then showed considerably decreased density of the bones suggesting osteomalacia He was admitted to the Marine Hospital, Staten Island, in December 1923, where he remained as a patient until November 1925 His fractured left arm was kept in a cast for 9 months before union occurred While in the hospital in August 1924 he fractured the left radius and in October 1925, the right humerus He was placed on a Bradford frame with traction to secure extension and his height increased to 5 feet 9 inches When he was allowed up he measured 5 feet 6 inches, after 30 minutes in an erect position Then he wore a supporting body brace The next deformities which appeared were a shortening of the neck, a sinking of the head, and a forward protrusion of the lower jaw Roentgenograms taken in the Marine Hospital showed osteomalacia involving the whole skeletal system While there he was given diets high in calcium and phosphorus, cod liver oil, calcium and phosphorus medications, thyroid extracts, epinephrin, heliotherapy, quartz lamp treatment, and irradiated milk, without noticeable improvement During his stay in the hospital he felt weak and suffered almost constantly from pain in his bones and joints

In the six weeks between his discharge from the Marine Hospital and his admission to Bellevue Hospital his pains gradually wore away and the urinary gravel nearly disappeared

Physical examination The general appearance can best be shown by the front and side views of the patient (Fig 1) He was well nourished His head showed exaggerated grooves and prominences of the calvareum and a protruding lower jaw The teeth were in good condition There were no evidences of infection of the throat The neck was short and thick with no enlargement of the thyroid The chest showed a marked prominence of the sternum The ribs impinged on the iliac crests The heart was normal in rate and rhythm There was an appendectomy scar in the right lower abdominal quadrant The external genitals were normal The spine was rigid, with marked kyphosis in upper dorsal region and with considerable tenderness on pressure in the lumbar region His ex-

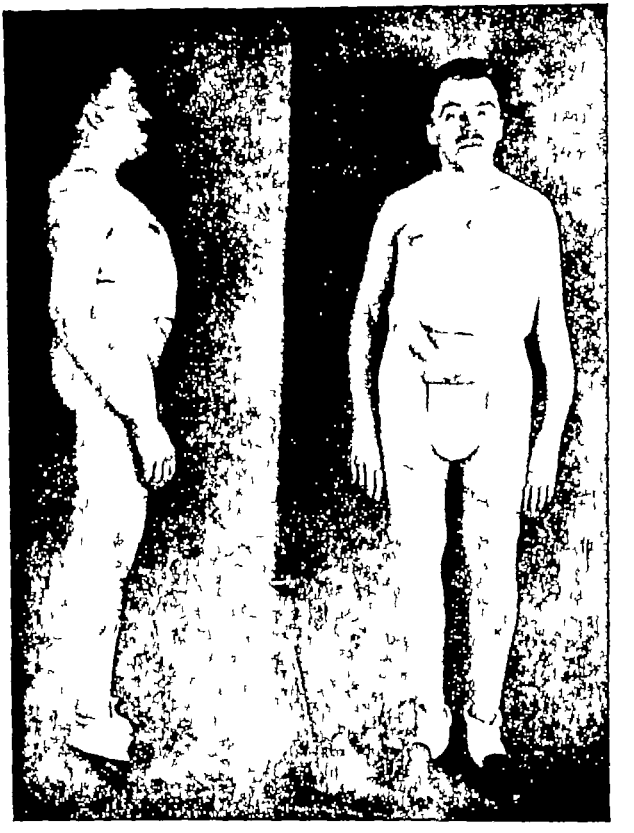

FIG 1 FRONT AND SIDE VIEWS OF THE PATIENT CHARLES M , JANUARY, 1926, SHOWING THE PROTRUDING JAW SHORT NECK, DEFORMED CHEST AND CONTOUR OF EXTREMITIES

FIG 2 ROENTGENOGRAM OF RIGHT HUMERUS AND ELBOW, JANUARY, 1926, SHOWING ATROPHY, FRACTURE IN LOWER END OF HUMERUS, AND A SMALL CYST

tremities showed bowing deformities in both arms due to old fractures with some tenderness on pressure over the bones The muscles generally were soft and flabby with apparent loss of tone The knee jerks were present but sluggish

Laboratory data The temperature varied between 98° and 99°F , the pulse between 70 and 90 per minute and the respirations between 18 and 24 per minute

FIG 3 ROENTGENOGRAM OF LEFT RADIUS AND ULNA JANUARY, 1926, SHOWING MARKED BOWING AND DEFORMITY

The blood pressure ranged from 110 to 125, systolic and 65 to 80 diastolic His weight remained between 64 5 and 66 8 kgm The urine was clear, amber, acid in reaction with specific gravity of 1,020 and was negative for glucose, albumen blood and casts The blood Wassermann was negative, the hemoglobin 95 per

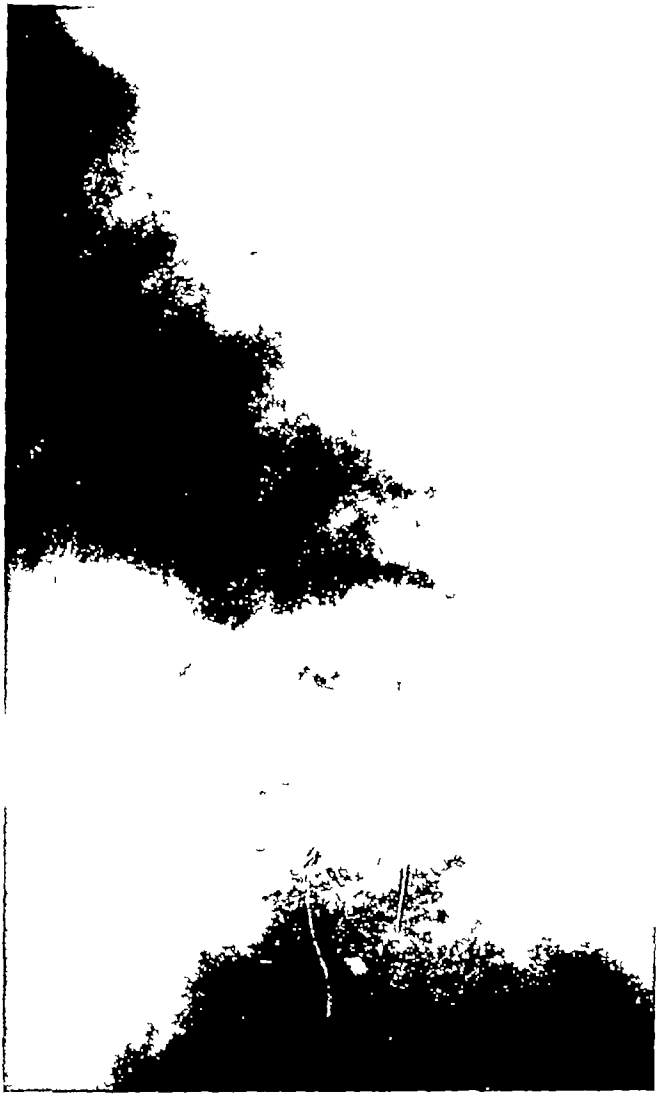

FIG 4 ROENTGENOGRAM OF LUMBAR SPINE, LATERAL VIEW, JANUARY, 1926, SHOWING CURVATURE, WIDENED INTERVERTEBRAL DISKS, AND NARROWED BODIES OF THE VERTEBRA

cent and the white blood count 7,400 with a differential count showing 62 per cent polymorphonuclears, 30 per cent lymphocytes, 6 per cent large mononuclears and 1 per cent each eosinophiles and basophiles The blood chemistry on January 20, 1926 was non protein nitrogen 36 mgm per 100 cc., uric acid 3 5 mgm sugar 98 mgm , serum calcium 14 5 mgm , serum phosphorus 3.3 mgm and carbon dioxide combining power 56 volumes per cent The blood on standing formed a soft, friable, dark red clot which retracted only slightly in 24 hours The basal metabolism was −8 to −17 per cent by Aub-Du Bois standards

Roentgenograms of the bones showed the following changes There was extensive bone atrophy with absorption of the cortex, a few cystic formations and marked bony deformities particularly in the pelvis and spine. The skull was involved in these changes Figure 2 shows the right humerus and elbow, figure 3 the left radius and ulna, and figure 4 a lateral view of the lumbar spine. The electrical reactions were, galvanic, K.C C 55 m a , A C C 60 m a and faradic 14 m.a These findings were about twice the amount of current required to produce a reaction normally and represent a considerable diminution in the electrical excitability of muscle and nerve.

Course in hospital After about 3 weeks of preliminary observations, exact metabolic balance studies were begun, and continued for 76 days, with accurately weighed diets and complete collection of all urine and feces The patient suffered at times from mild pains, especially on moving about in bed He remained in bed during the entire period of observation He received a diet of 2500 calories containing 75 grams protein, and was in a slightly positive nitrogen balance throughout The calcium in the food was varied from 0 5 to 1.2 grams per day He required 0 7 gram of calcium (expressed as calcium) daily to maintain balance and with an intake of 0.5 gram per day showed a negative balance Three hundred and eighty units of parathormone were given between February 16 and March 2 with a maximum daily dosage of 40 units The patient was more uncomfortable during this medication and hence it was stopped. Moderate constipation was experienced during the first month in the hospital which was readily relieved by strychnine and agar agar The patient's general condition improved and on April 23, 1926 he was transferred to the metabolism ward of the Massachusetts General Hospital in the care of Drs Aub and Bauer

METHODS

The calcium and phosphorus intakes were calculated from Sherman's food table as given by Rose (3) Seven diets which duplicated the diets for one day of each period were analysed for calcium and phosphorus It was found that the calculated amounts of calcium and phosphorus in the diets for the period varied both above and below those of the diets analysed but the average for the daily diets fell within 5 per cent of the amounts found in the diet which was analysed Therefore, we feel that the calculated intakes represent accurately the actual

FIG 4 ROENTGENOGRAM OF LUMBAR SPINE, LATERAL VIEW, JANUARY SHOWING CURVATURE, WIDENED INTERVERTEBRAL DISKS, AND NARROWED BODIES OF THE VERTEBRA

amounts of these minerals ingested. The calcium in the urine was determined by the method of Shohl and Pedley (4) and the phosphorus by the method of Fiske and Subbarow (5) The feces was dried, digested with sulfuric and nitric acids and the calcium and phosphorus determined in the same way as in the urine The serum was estimated by the method of Kramer and Tisdall as modified by Clark and Collip (6) and the serum phosphorus by the method of Fiske and Subbarow (5) Table 1 contains the blood calcium and phosphorus determinations and the other significant data concerning the calcium and phosphorus balances during the periods of observation

COMMENTS

From the clinical and roentgenological studies it seems evident that this is a case of osteitis fibrosa cystica although the differentiation from osteomalacia is not easy Clinically he had a long history of progressive skeletal deformities with frequent fractures which healed slowly Roentgenograms showed general rarefaction of the bones with no proliferation and some cyst formation

At the present time bone is considered an active tissue that is constantly being built up and broken down by osteoblasts and osteoclasts and a part of an interacting system made up of soft tissues, blood, and bone In osteitis fibrosa cystica, as well as in osteomalacia, osteogenesis imperfecta, and rickets, the essential nature of the pathological disturbance is the laying down of a type of bone deficient in lime salts, called osteoid tissue, in place of normal bone The similarity of the pathological changes in the skeleton in these diseases has led many to regard them as a single disease with varying degrees of intensity and with different localizations

The causes of these conditions have usually been classified as exogenous or endogenous The first group includes malnutrition, lack of specific food factors such as vitamine D, and diets deficient in calcium In the endogenous group fall repeated pregnancies and protracted lactation, certain pathological processes such as osteomata and myositis ossificans, and disturbances in the glands of internal secretion, particularly the ovaries and parathyroids McCrudden (2) has discussed most of these factors

We have found no studies of the mineral balance of patients with

osteitis fibrosa cystica [2] Osteomalacia, however, has been extensively studied in this respect The most constant findings in osteomalacia are a negative calcium balance and a lowered calcium content of the blood, even when ingesting amounts of calcium which would be adequate for a normal individual A few cases are reported with elevated blood calcium (2)

The rôle of the parathyroid in calcium metabolism is now well recognized

a Hyposecretion, either infantile (tetany) (7), postoperative, or idiopathic, is marked by low blood calcium with elevated blood phosphorus, and increased muscle and nerve irritability as evidenced by the electrical reactions and the occurrence of convulsions

b Hypersecretion, studied by the use of a potent extract of parathyroids (8), is distinguished by elevation of blood calcium, a lowered blood phosphorus (later followed by elevation if the extract is continued), and by a negative calcium balance at the expense of the bone calcium (9)

Our patient presented a number of prominent features

1 Blood calcium Throughout the period of observation the level was elevated ranging from 13 4 to 16 5 mgm per 100 cc of blood, but usually between 15 0 and 16 0 mgm The normal range is between 9 and 11 mgm (10) This finding is in contrast to the usual level in osteomalacia (11) which is generally lower than normal They correspond to the figures obtained in animals which received a potent parathyroid extract Clinically Hunter and Aub (12) found high levels during periods of parathyroid administration in the treatment of lead poisoning

2 Blood phosphorus The determinations all fell between 1 1 and

[2] Since these studies were made, three reports of the mineral balance in osteitis fibrosa cystica have appeared 1 Gold, Wien Med Wochenschrift, 1927, lxxvii, 1734, 2 Barr, Bulger, and Dixon, J A M A , 1929, xcii, 951, 3 Wilder, Endocrinology, 1929, xiii, 231 The chemical findings are in essential agreement with those presented by this patient All three had tumors of the parathyroid bodies which were removed with clinical improvement Wilder's paper contains an excellent discussion of the rôle of the parathyroid bodies in osteitis fibrosa cystica with a collection of the cases reported in the literature

3 3 mgm per 100 cc and mostly below 2 5 mgm The normal level is between 3 0 and 4 0 (13) This depression in the phosphorus level in the blood has been mentioned by Collip following the administration of parathyroid extract (8) On continued administration of parathyroid extract the animals showed rising phosphorus levels which were marked just before death

3 Mineral balances The intake of calcium and phosphorus was entirely supplied from the food A daily intake of 0 4 gram of calcium (expressed as calcium) is sufficient to maintain a normal individual in balance (14) Our patient required 0 7 gram per day to maintain him in calcium equilibrium and on 0 5 gram per day he had a definite negative calcium balance The facts with regard to phosphorus balances are vague Our patient showed a positive balance for five periods and a negative balance in the last two periods No explanation for this shift in balance can be offered

4 Mineral excretion The normal subject on a general balanced diet excretes in the feces from 70 to 90 per cent of the total calcium eliminated and the remainder in the urine (15) On the other hand our subject excreted only 10 to 30 per cent in the feces and the greater amount in the urine The low calcium excretion in the feces suggests efficient absorption from the intestine

5 Parathormone administration All the medications which have been recognized as of value in treating osteomalacia had been used without success While he was under careful observation we administered parathormone in small doses, for diagnostic purposes He received 380 units over a period of 15 days The clinical effects were striking He complained of definite increase of pain all over his body, especially on motion There was in addition, a slight elevation in the blood calcium The medication was then stopped

6 Electrical reactions The muscles generally were flabby and poor in tone The electrical reactions revealed a marked reduction in excitability of muscle and nerve This is the exact opposite of the response obtained in hypoparathyroidism (16)

7 Nature of blood clot The blood clot differed from the usual normal clot It slowly formed a dark red, very friable clot with very little clot retraction Serum, free from red cells, could not be obtained except by centrifugalization This is in keeping with the find-

ings of Mellanby (17), that an increase in blood calcium concentration lengthens the coagulation time

Our patient then presents a picture which agrees in its essentials with that produced by the excessive administration of parathyroid extract and opposite to that found in hypoparathyroidism These considerations and the finding of parathyroid tumors in patients with osteomalacia and similar bone disturbances (18) led us to the conclusion that the underlying basis for the osteitis fibrosa cystica in our subject was a hyperactivity of the parathyroid bodies

It was obvious that a search for some abnormality of the parathyroid glands was the next step indicated At the closing of our metabolism ward for the summer the patient was transferred to the care of Drs Aub and Bauer at the Massachusetts General Hospital for further studies of his calcium metabolism and a consideration of the advisability of removing one or more of his parathyroid glands

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A CASE OF OSTEITIS FIBROSA CYSTICA (OSTEOMALACIA?) WITH EVIDENCE OF HYPERACTIVITY OF THE PARATHYROID BODIES METABOLIC STUDY II[1]

By WALTER BAUER,[2] FULLER ALBRIGHT[3] AND JOSEPH C AUB

(From the Medical Clinic of the Massachusetts General Hospital, Boston)

(Received for publication February 5 1929)

INTRODUCTION

In a previous paper (1) we have pointed out certain characteristic responses in the calcium and phosphorus metabolisms resulting from parathormone[4] administration to essentially normal individuals In the present paper, similar studies will be reported on a patient who presented a condition suggestive of idiopathic hyperparathyroidism

CASE HISTORY

The patient, Mr C M , sea captain, aged 30, was transferred from the Bellevue Hospital Service to the Special Study Ward of the Massachusetts General Hospital through the courtesy of Dr Eugene F DuBois, for further investigation of his calcium metabolism and for consideration of parathyroidectomy His complete case history has been reported by Hannon, Shorr, McClellan and DuBois (2) It describes a man invalided for over three years with symptoms resulting from a generalized skeletal decalcification (See x rays, figs 1 to 4)

[1] This is No VII of the series entitled Studies of Calcium and Phosphorus Metabolism from the Medical Clinic of the Massachusetts General Hospital

Resident Physician Massachusetts General Hospital

[3] Research Fellow Massachusetts General Hospital and Harvard Medical School

[4] Parathormone is Eli Lilly and Co s trade name for Collip s parathyroid extract

FIG 2 X RAY OF RIGHT SHOULDER SHOWING OLD FRACTURE AT THE LOWER END OF THE HUMERUS. ABSENCE OF MOST OF THE BONE TRABECULAE IN THE MIDDLE HALF WITH THINNING OF THE CORTEX AND SLIGHT BULGING OF THE SHAFT ALSO INDEFINITELY DEFINED CYSTIC AREAS IN THE LOWER THIRD

FIG 4 X RAY OF THE LEFT HUMERUS SHOWING WELL DEFINED ATROPHY WITH THINNING OF THE CORTEX AND IRREGULARITY IN THE HEAD OF THE HUMERUS IN THE REGION OF THE TUBEROSITY

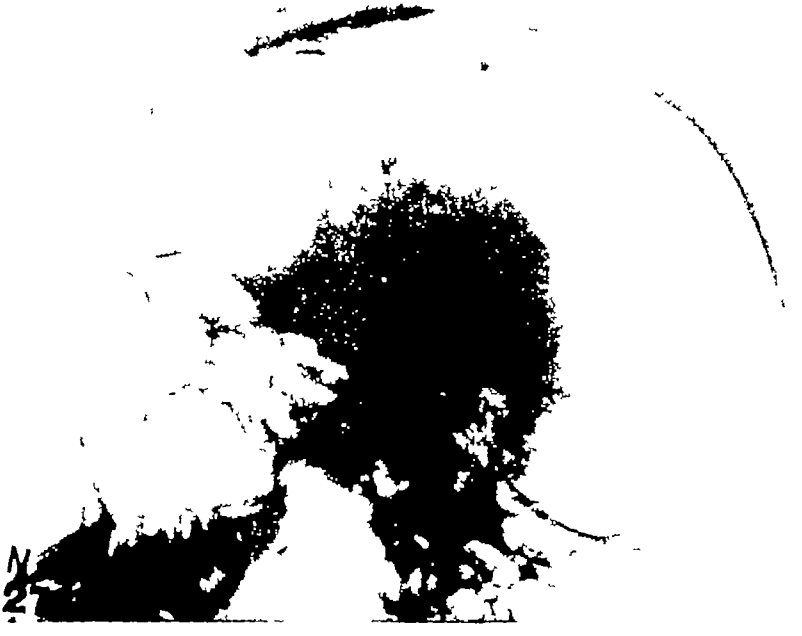

FIG 5 FILMS OF THE SKULL SHOW THE POSTERIOR PORTION OF THE CALVARIUM TO BE THINNER THAN USUAL

The bone in the frontal region appears to be thickened and has a rather mottled appearance

EXPERIMENTAL DATA

The investigation, in accordance with the principles set forth in previous papers (3), consisted of complete calcium, phosphorus and nitrogen metabolism studies as well as frequent determinations of the serum calcium and serum phosphorus Whereas our previous studies have been confined almost entirely to low calcium intakes, in this study some periods on a high calcium diet were also included for three reasons In the first place, we wished to confirm the findings of the Cornell group, who had studied this patient while on a relatively high calcium diet Secondly, it seemed essential from a therapeutic standpoint to determine whether a positive calcium balance could be maintained on a high calcium diet Lastly, because of the patient's marked skeletal decalcification, it was not considered wise to study him for more than a very short period on a low calcium diet

During the patient's stay in the Hospital, two normal parathyroid glands were removed by Dr Edward P Richardson Our studies include periods of high and low calcium diet before and after the operations

The methods employed in the collection of the excreta and in the analyses of the material have been given in previous papers (3 and 4) The details of the operations and the pathological reports of the tissues removed are given in the appendix (q v) The essential point is that two normal appearing parathyroid glands were removed at operation

RESULTS

In table 1 and charts 1A, 1B, and 1C are found the data for the calcium, phosphorus and nitrogen excretion Each study period is three days unless otherwise indicated In table 1 are also included the serum calcium and serum phosphorus values

A Serum calcium and serum phosphorus

On examination of these blood findings one notes that the serum calcium is markedly elevated above normal and that the serum phos phorus is considerably reduced below normal, indeed relatively more than the serum calcium is elevated Such a fall of the blood phos phorus we have found to be the case on administration of parathormone, provided that the serum calcium does not rise sufficiently high to produce a secondary phenomenon which is associated with a marked increase of the serum phosphorus The serum calcium in this patient was not sufficiently high to produce this phenomenon and the low serum phosphorus is in accordance with the findings in patients receiving parathormone The removal of the two parathyroid glands was apparently without effect on the blood findings

B Metabolism findings

The discussion of the metabolic findings (table 1 and charts 1A, 1B and 1C) will be divided into four parts

a A comparison of the findings before operation, while the patient was on a low calcium diet, with those of normal individuals on a similar diet

b A comparison of the findings in respect to both calcium and phosphorus metabolism before operation while the patient was on a low calcium diet with those of an individual receiving 100 units of parathormone per day

Period	Weight	Intake	Calcium: Output Urine	Calcium: Output Feces	Calcium: Output Total	Calcium: Intake	Calcium: Balance	Calcium: P equivalent of Ca balance	Phosphorus: Output Urine	Phosphorus: Output Feces	Phosphorus: Output Total	Phosphorus: Intake	Phosphorus: Balance	Phosphorus: Theoretical balance	Nitrogen: Output Urine	Nitrogen: Output Feces	Nitrogen: Output Total	Nitrogen: Intake	Nitrogen: Balance	Nitrogen: P equivalent of N balance	Blood serum: Day of period	Blood serum: Calcium	Blood serum: Phosphorus	Remarks
	kgm	gm	gm	gm	gm	gm	gm	gm	gm	gm	gm	gm	gm	gm	gm	gm	gm	gm	gm	gm		mgm	mgm	
1 } * 2 }	64 8	5 165	1 44	0 74	2 18	3 22	+1 04	+0 53	3 02	0 58	3 60	4 02	+0 42	+0 32	32 9	3 0	35 9	32 1	−3 8	−0 21	1	14 1	2 1	
																						14 3	1 4	
3	64 7	5 822	1 09	0 13	1 22	0 30	−0 92	−0 48	2 15	0 22	2 37	2 09	−0 28	−0 28	24 1	2 3	26 4	29 9	+3 5	+0 20				
4		5 820	1 34	0 07	1 41	0 31	−1 10	−0 57	2 25	0 24	2 49	2 11	−0 38	−0 49	25 8	3 3	29 1	27 6	−1 5	−0 08		14 0	2 0	
5	64 2	5 820	1 51	0 27	1 78	0 31	−1 47	−0 77	2 27	0 27	2 54	2 11	−0 43	−0 43	29 6	3 8	33 4	27 6	−5 8	+0 30		14 2	3 5	
6	64 4	5 840	1 50	0 30	1 80	1 72	−0 08	−0 04	2 46	0 24	2 70	3 10	+0 40	−0 10	28 0	2 7	30 7	29 9	−0 8	−0 06				
7	62 6	6 299	1 55	0 41	1 96	3 22	+1 26	+0 65	2 62	0 28	2 90	3 40	+0 50	+0 92	28 2	1 6	29 8	34 6	+4 8	+0 27				
8†	63 8	3 967	2 24	0 50	2 74	2 05	−0 69	−0 36	4 91	0 34	5 25	1 98	−2 71	−2 80	49 0	3 4	52 4	9 7	−42 7	−2 44		14 5	1 6	First parathyroidectomy
9	63 2	4 302	1 02	0 09	1 11	1 01	−0 29	−0 05	2 86	0 36	3 22	0 82	−0 41	−0 43	28 5	2 4	30 9	24 3	−6 6	−0 38	1	14 1	1 9	
10	63 2	5 012	1 46	0 67	2 13	2 61	+0 48	+0 25	2 36	0 52	2 88	3 44	+0 56	+0 43	22 9	3 0	25 9	29 0	+3 1	+0 18	2	14 3	4 7	
11	63 8	5 694	1 68	0 83	2 51	5 50	+2 99	1 55	3 11	0 62	3 73	5 50	+1 77	1 57	33 5	2 2	35 7	36 0	+0 3	+0 02				
12	62 0	2 450	1 53	1 09	2 62	House diet			5 43	0 88	6 31	House diet			33 6	3 7	37 3	House diet			2	14 6	2 2	
12‡						House diet																		
																					5	15 3	1 8	
																					10	14 0	2 4	Second parathyroidectomy on ninth day of period
																					13	15 1	2 1	
																					17	13 9		
																					20	13 4	2 3	
13 } * 14 }	63 5	7 334	1 41	0 16	1 57	0 29	−1 28	−0 66	2 74	0 34	3 08	2 45	−1 63	−0 64	26 3	4 2	30 5	30 8	+0 3	0 02	3	13 8	2 1	
15	63 7	7 011	1 58	0 33	1 91	3 40	+1 49	+0 77	2 95	0 57	3 52	4 63	+1 11	+1 40	29 5	3 7	33 2	44 1	+10 9	+0 63	3	13 8	1 8	
16 } * 17 }	65 6 65 4	7 416	1 67	0 59	2 26	4 57	+2 31	+1 09	3 63	0 71	4 34	6 57	+2 23	+1 63	36 7	5 7	42 4	52 7	+10 3	+0 54	2	15 0	2 0	
18	65 8	7 167	1 53	0 93	2 46	5 16	+2 70	+1 30	3 48	0 89	4 37	6 23	+1 86	+1 88	40 4	3 5	43 9	54 0	+10 1	+0 58	2	13 6		
19		7 639	1 76	0 82	2 58	5 18	+2 60	+1 35	4 27	0 89	5 16	6 87	+1 71	+1 76	41 4	6 4	47 8	55 0	+7 2	+0 41	2	13 8	2 7	
20	66 0	7 879	1 50	0 80	2 30	5 17	+2 87	+1 49	3 30	0 67	3 97	6 46	+2 49	+2 12	41 5	4 6	46 1	57 0	+10 9	+0 63				
21	66 2	7 623	2 22	0 83	3 05	6 29	+3 24	+1 67	4 44	1 07	5 51	7 35	+1 85	+1 88	48 6	5 7	54 3	58 0	+3 7	+0 21	1	13 8	2 4	
22		8 354	2 07	0 70	2 77	6 11	+3 34	+1 73	4 31	1 15	5 46	6 74	+1 28	+1 46	42 1	5 6	47 7	43 0	−4 7	−0 27				
23		6 143	1 22	0 42	1 64	1 39	−0 25	−0 13	3 28	0 53	3 81	3 73	−0 08	−0 58	32 9	4 9	37 8	30 0	−7 8	−0 45	1	13 1	2 5	
24	66 4	5 611	1 15	0 23	1 38	1 61	−0 23	+0 12	2 86	0 37	3 23	3 24	+0 01	+0 13	28 0	3 4	31 4	31 6	+0 2	−0 01				
25		8 163	2 02	0 68	2 70	7 51	+4 81	+2 49	4 10	1 15	5 25	8 15	+2 90	+3 30	39 4	5 5	44 9	59 0	+14 1	+0 81	2	13 3	2 4	
26		8 181	2 49	1 00	3 49	0 90	−2 59	+1 34	4 87	1 17	6 04	8 75	+2 71	+2 01	52 6	4 7	57 3	69 0	+11 7	+0 67				
26A§																								
																					20	13 8	2 9	
																					29	13 9	3 3	
																					39	13 6	3 2	
27	72 2	4 344	1 11	0 13	1 24	0 29	−0 95	−0 49	2 60	0 53	3 13	2 30	−0 83	−0 79	34 0	4 1	38 1	32 8	−5 3	−0 30	1	13 7	1 9	
28†	73 6	15 369	3 54	0 58	4 12	9 14	+5 02	+2 62	6 52	1 06	7 58	12 19	+4 61	+4 08	71 5	15 1	86 6	112 0	+25 4	+1 46	5	14 0	1 7	

* Because of overlapping of feces, two periods have been averaged.
† Six day period instead of three-day period
‡ Period 12A consists of 21 days during which patient was on house diet.
§ Period 26A consists of 50 days during which patient was on house diet

c A comparison of the findings while the patient was on a high calcium diet with the findings of the Cornell group (2)

d A comparison of the findings, during both high and low calcium periods before operation, with similar periods after operation

In a previous paper (3) giving the calcium excretion of normal individuals on a low calcium diet, it was pointed out that before

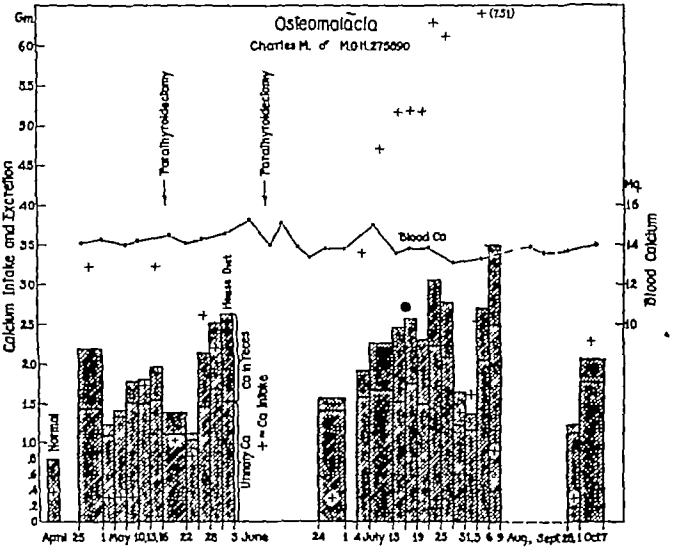

CHART 1A. SHOWING GRAPHICALLY THE CALCIUM METABOLISM DATA FROM TABLE 1

quantitative comparisons could be made with regard to the calcium metabolism between individuals, factors had to be introduced which took into account the sex, age, weight, activity, acid base balance of diet, proportion of other bases in diet, and phosphorus metabolism This patient (male, age 30, weight 64 kgm) compares favorably with the controls (all male, average age 41, average weight 62 kgm) The diet of the patient was picked from the same limited menu as that

of the control patients so that the acid-base values and cation contents should be approximately equal As regards activity, this patient was in bed until periods 26 and 28 as compared with mild activity on the part of the controls Except for period 7, the patient remained essentially in nitrogen balance In table 2, the average values for the three low calcium periods before operation (periods 3, 4 and 5) are compared with the average values of the control series (3) One

TABLE 2

Comparison of preoperative period of C M with controls

	Calcium				
	Output			Intake	Balance
	Urine	Feces	Total		
	gm	*gm*	*gm*	*gm*	*gm*
Control series (3)	0 19	0 60	0 79	0 33	−0 46
Average of periods 3, 4, and 5 on Mr C M	1 31	0 19	1 50	0 31	−1 29

TABLE 3

Comparison of preoperative periods of C M with a normal individual receiving parathormone

	Calcium					
	Output			Intake	Balance	Serum calcium
	Urine	Feces	Total			
	gm	*gm*	*gm*	*gm*	*gm*	*mgm per 100 cc.*
Patient receiving 100 units of parathormone daily (average of 4 periods)	1 33	0 45	1 78	0 34	−1 44	11 5–12 8
Average of periods 3, 4, and 5 on Mr C M	1 31	0 19	1 50	0 31	−1 29	13 1–15 3

notes from table 2 that the negative calcium balance on a low calcium diet is markedly increased in this patient and that this increase is entirely due to an increased urinary calcium excretion, the fecal calcium excretion being actually decreased

It is now of interest to compare the findings in this patient with those of an essentially normal individual receiving 100 units of parathormone a day (Mr W S (1)) The calcium figures are shown in table 3 and indicate that the calcium metabolism of this patient while on a low

calcium diet is qualitatively and quantitatively similar to an individual receiving 100 units of parathormone

From table 1 and chart 1B, it will be noted that phosphorus was lost from the body coincident with the calcium loss It will be further noted that an unusually large proportion of the phosphorus

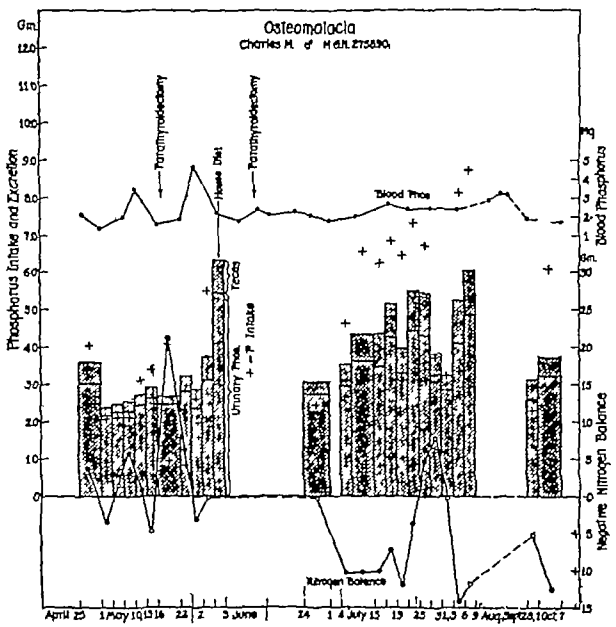

CHART 1B REPRESENTING THE PHOSPHORUS METABOLISM DATA FROM TABLE 1

was excreted in the urine In chart 1C, if one makes the assumption that the calcium and phosphorus losses represent tertiary calcium phosphate withdrawn from the bones, this phosphorus loss is shown to be closely in agreement with the calcium loss The "theoretical phosphorus balance" in chart 1C is the sum of the phosphorus equivalent of the nitrogen balance (N/P in protein = 17 4) and

the phosphorus equivalent of the calcium balance (Ca/P in tertiary calcium phosphate = 1 93)[5] and has been discussed at length in paper 3 of this series (1) The close agreement of the actual and

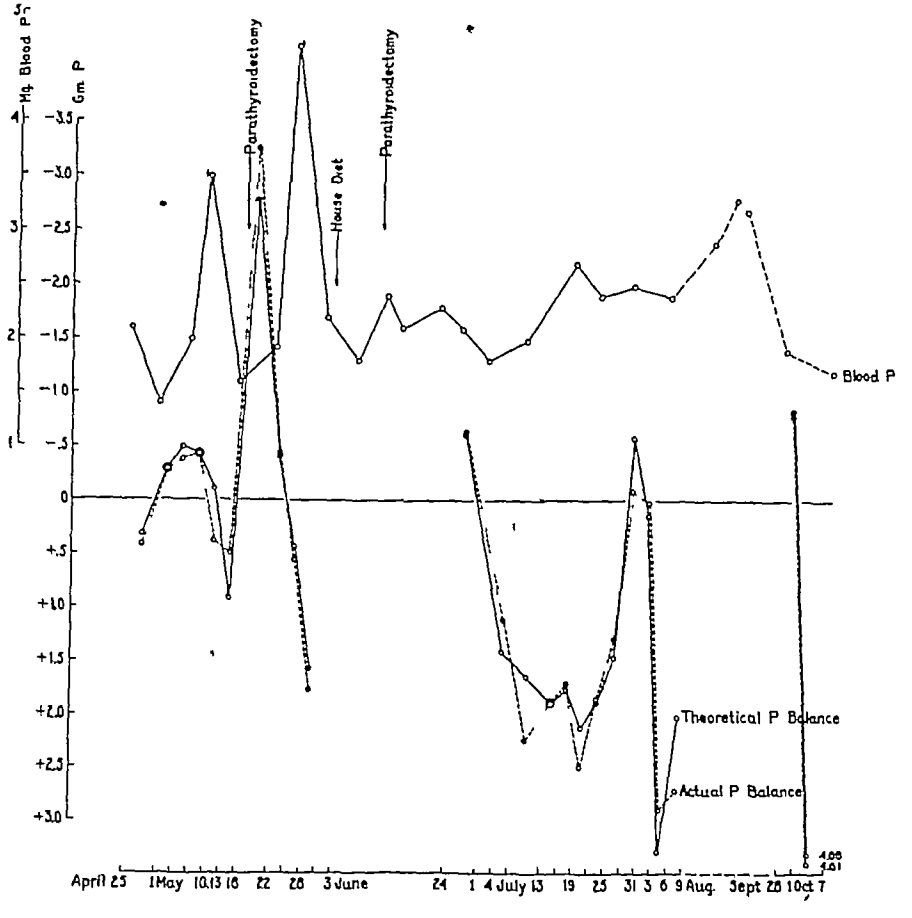

CHART 1C COMPARISON OF THE ACTUAL AND THEORETICAL PHOSPHORUS BALANCES

theoretical phosphorus balances in chart 1C is consistent with a constant degree of hyperparathyroidism, and is in contradistinction to what takes place when shifts are made from a lesser to a greater degree of hyperparathyroidism by injection of parathyroid extract (1)

[5] The factor 1 93 was used in this paper and represents the ratio of Ca/P in $Ca_3(PO_4)_2$ In paper 3 of this series (1), the factor 2 23 was used which represents the ratio of Ca/P in bone

Thus we may conclude that the calcium and phosphorus metabolism of this patient before operation was consistent with that of persons receiving large doses of parathyroid extract

TABLE 4

Comparing C M on high calcium intake as studied in two clinics

	Calcium					Nitrogen balance
	Output			Intake	Balance	
	Urine	Feces	Total			
	gm.	gm.	gm.	gm.	gm.	gm.
Average of periods 1, 2 and 7 on Mr C M	1 48	0 64	2 12	3 22	+1 10	+8 6
Average of 3 periods of investigations by Cornell group (2) on Mr C M	1 98	0 41	2 39	2 72	+0 33	−0 9

TABLE 5

Comparison of C M on high and low calcium intake before and after operation

	Periods	Calcium					Nitrogen balance
		Output			Intake	Balance	
		Urine	Feces	Total			
		gm.	gm.	gm.	gm.	gm.	gm.
Before operations	Average of 1, 2 and 7	1 48	0 64	2 12	3 22	+1 10	+8 6
	Average of 3, 4 and 5	1 31	0 19	1 50	0 31	−1 29	−1 3
After operations	15	1 58	0 33	1 91	3 40	+1 49	+10 4
	Average of 13 and 14	1 41	0 16	1 57	0 29	−1 28	0 3

It was extremely important for the patient's welfare to know whether he could be kept on a positive calcium balance by dietary measures Therefore, he was studied on a high calcium diet [6]

In table 4 are given these data with those obtained by the Cornell

[6] The principles suggested by later investigations (1) were not understood at the time of this study, or else a high phosphorus diet would have been tried as well as a high calcium diet

the phosphorus equivalent of the calcium balance (Ca/P in tertiary calcium phosphate = 1 93)[5] and has been discussed at length in paper 3 of this series (1) The close agreement of the actual and

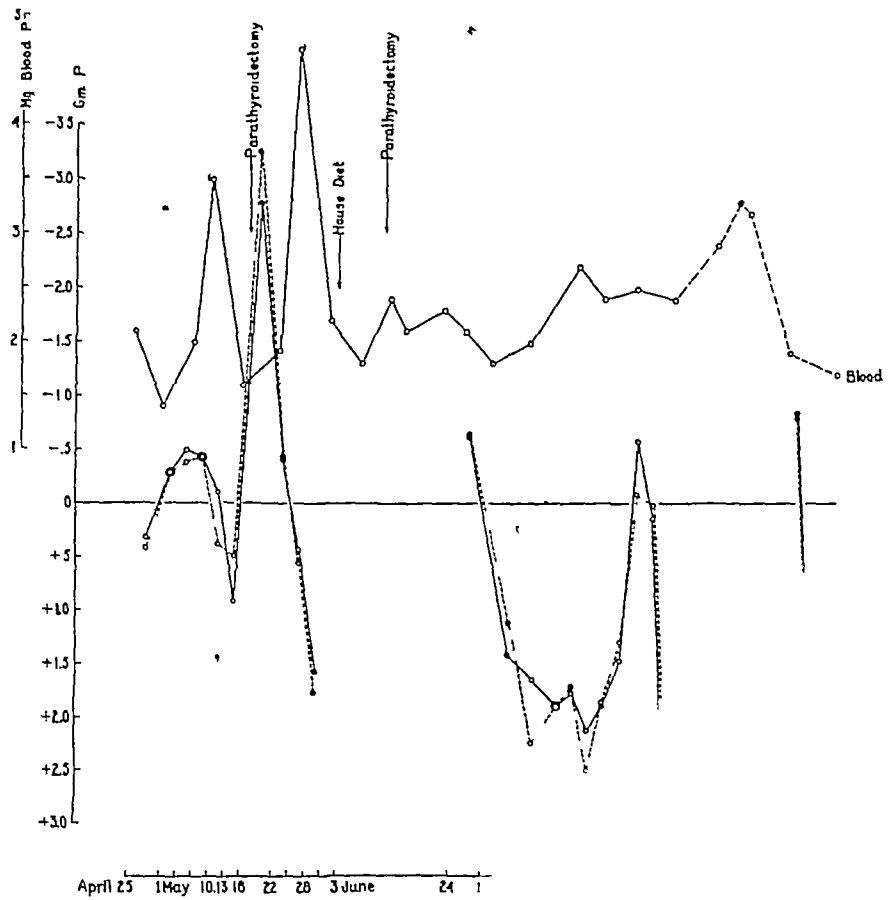

CHART 1C COMPARISON OF THE

4 1923 Klemperer (12)—tumor of parathyroid with multiple bone metastases from carcinoma of breast
5 1924 Ritter (13)—2 year old female—enlargement of four parathyroids with rickets
6 1925 Ferrero, J and Sacerdote, G (14)—65 year old female—parathyroid tumor with benign metastases of parathyroid tumor to femur and temporal bones

Of the 88 cases of bone disorders associated with parathyroid lesions, 14 showed tumors and the rest hyperplasia of the parathyroid glands Of the cases in which hyperplasia was found, 21 were associated with osteomalacia, 15 with osteitis fibrosis, 3 with rickets, 6 with senile osteomalacia, and 28 with senile osteoporosis In the cases of parathyroid tumors, 9 were associated with osteitis fibrosa, 1 with osteomalacia, 1 with benign parathyroid tumor metastases to the temporal and femur bones, and 1 with multiple bone metastases from a breast carcinoma.

Table 6 taken from the literature shows in summary form various types of conditions which have been examined for question of associated parathyroid pathology and the number in which pathological glands were found Thus, in 46 normal cases examined, hypertrophy was present in 4 In 19 cases of rickets 1 showed hypertrophy The parathyroids were normal in 32 cases of senile osteoporosis, 5 cases of osteitis deformans and 8 cases of senile osteomalacia Of 54 cases of osteomalacia examined, 25 showed hypertrophy One normal case presented a large cystic parathyroid tumor

Except for Mandl's case, all the pathological parathyroids associated with bone disorders were found at autopsy The occurrence of a bone lesion and a lesion of the parathyroids together does not necessarily mean that the two are interrelated, unless there is some clinical evidence of disfunction of the parathyroid glands such as an alteration of the serum calcium or calcium excretion In Mandl's case and the one here reported this pre-mortem evidence is present Unlike Mandl, however, we were unable to find a pathological parathyroid gland Our failure to find an abnormal gland, on the other hand, does not prove that one does not exist

In a previous paper evidence has been introduced which suggested that the increased calcium excretion and the increased serum calcium in hyperparathyroidism may be dependent on an increased phosphorus excretion and a depletion of the body's fluid phosphorus (1) In this connection it is of interest to note the picture which results when the body's supply of phosphorus is depleted by insufficient phosphorus intake This experiment has been performed by nature on cows and reported recently by Palmer and Eckles (22) In certain regions where the grass has a very low phosphorus content, cows develop a

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that in an individual receiving large doses of parathormone and diametrically opposite to that in a patient with parathyroid tetany, we feel justified in concurring in the diagnosis of hyperparathyroidism suggested by Dr Eugene F DuBois

8 It is pointed out that a high phosphorus diet might be more efficacious from a therapeutic standpoint than a high calcium diet in this case

APPENDIX

First operation by Dr E P Richardson. "Right parathyroidectomy Curved incision downward over carotid sheath turning across median line above the suprasternal notch Sterno-mastoid retracted outward and prethyroid muscles divided, exposing anterior surface of thyroid which was of normal size and even consistency but pale The carotid sheath was retracted outward The right lobe of the thyroid was then turned toward the median line Its posterior surface and surrounding areolar tissue was carefully searched for parathyroids The inferior thyroid artery and recurrent laryngeal nerve, crossing the front was exposed in this dissection The dissection was carried toward the median line, The inferior thyroid artery entered about the middle of the posterior lobe There was a large anastomotic branch joining the superior thyroid No parathyroid tissue was found until after the division of the inferior artery Just to the median side of this point there was a small vascular area 6 mm in diameter, deeper red than the remainder of the thyroid lobe This area was flattened and encapsulated It was dissected off and thought to be parathyroid Slightly to the median line from this another smaller area, not so distinctly encapsulated, was removed Thyroid replaced, muscles sutured Wound closed without drainage"

Histological report "Parathyroid glands Microscopic examination shows one nodule out of five having the structure of a parathyroid gland"

Second operation by Dr E P Richardson "Exploration of thyroid Curved incision extending across the neck partly through the old scar and exposing the thyroid lobe Thyroid lobe turned towards the median line, the posterior aspect carefully dissected No evidence of adenoma of parathyroid No structures resembling normal parathyroid glands were seen Since the parathyroid removed on the other side resembled normal fat, six lobules of fat were removed from the region of the posterior aspect of the thyroid One of these lying adjacent to the inferior thyroid artery at about the middle of the glands seemed to be a possibl parathyroid gland Wound closed"

Histological report "Region of parathyroid Microscopic section of six specimens showed one which is labelled 'inferior thyroid artery' with the str of the parathyroid gland The remainder are composed of lymphoid ti fat"

A CASE OF OSTEITIS FIBROSA CYSTICA (OSTEOMALACIA?) WITH EVIDENCE OF HYPERACTIVITY OF THE PARATHYROID BODIES METABOLIC STUDY III

By W S McCLELLAN[1] AND R. R. HANNON

(From the Russell Sage Institute of Pathology in affiliation with the Second Medical (Cornell) Division of Bellevue Hospital, New York)

(Received for publication July 15, 1929)

The case history of the patient C M and observations of his calcium and phosphorus metabolisms both before and after the removal of two parathyroid bodies have been presented in Papers I and II of this series (1, 2) After the patient left the Massachusetts General Hospital he spent one month at home and then was readmitted to the metabolism ward of the Russell Sage Institute of Pathology, November 1, 1926 He returned for a period of stretching to see if his deformities could be completely or partially corrected During this stay in the hospital further observations were made to see the effect of various diets and medicines on his mineral metabolism

CLINICAL COURSE

After roentgenograms were taken to compare with the earlier findings, the head of the patient's bed was elevated to an angle of 30 degrees and traction was applied by weights attached to a leather collar The traction was continued for four and one-half months and during this time he was not allowed to sit up He maintained his physical condition by various gymnastic exercises daily during the time when his bed was lowered His height on admission was 168 cm The maximum height during the period of stretching was 170 cm He first sat up by himself April 1, 1927 and during the next month he increased the amount of activity daily His height then was 168 cm He wore a supporting leather jacket and on discharge from the ward, April 29, 1927, he could walk easily with the aid of a cane.

[1] National Research Fellow in Medicine

The roentgenograms of November 4, 1926 revealed thinning of the cortex of the long bones, healed recent oblique fracture of lower end of the right humerus in good position and an old healed fracture of the upper third of the left ulna with slight deformity The skull revealed numerous decalcified areas A large cyst in the right femur described during his previous admission was somewhat smaller The dorsolumbar spine showed diminution of the width of the vertebrae with pressure atrophy and slight kyphosis When these plates were compared with plates taken ten months previous there seemed to be some increased density of the bones On April 27, 1927 the osseous system was the same as described on November 4, 1926

EXPERIMENTAL RESULTS

The changes, which occurred in the calcium and phosphorus balances and the medicines given are presented in table 1 The studies cover 14 consecutive periods between November 15, 1926 and April 17, 1927 The results are reported as the average daily intake and output for each period The methods applied to these studies were the same as used for our previous observations (1)

During the first period he received approximately 1 0 gram of calcium per day and both the calcium and phosphorus were constituents of the foods eaten This period was obtained as a comparison with previous studies reported in Paper I (1) It revealed a definite positive balance for both calcium and phosphorus The positive calcium balance was explained by the unusually small amount of calcium excreted in the feces, which is much lower than any other observations on this subject

In period II he received subcutaneous injections of surgical pituitrin, 0 5 cc twice daily, for 6 days during the first half of the period He remained in positive calcium balance but a definite increase in the calcium in the feces was noted

In period III, 3 grams of calcium lactate which contained 0 4 gram of calcium were added to the diet daily without any increase in calcium retention No change in phosphorus intake was made There was a definite increase in the calcium excreted in both urine and feces

In the next period cod liver oil, 24 cc per day was added to the diet One cubic centimeter of the cod liver oil contained by analysis 0 002

TABLE I

Calcium and phosphorus balances 1926–27 Reported as daily averages for each period

Period	Number of days	Calcium					Phosphorus					Remarks
		Intake	Output			Balance	Intake	Output			Balance	
			Urine	Feces	Total			Urine	Feces	Total		
		grams	grams	grams	grams	grams	grams	grams	grams	grams	grams	
I	10	1 111	0 508	0 062	0 570	+0 541	1 272	1 017	0 122	1 139	+0 133	No medication
II	15	1 137	0 524	0 531	1 055	+0 082	1 321	1 053	0 199	1 252	+0 069	Pituitrin 1 0 cc daily for six days
III	10	1 454	0 651	0 746	1 397	+0 057	1 296	1 046	0 226	1 272	+0 024	Calcium lactate 3 0 grams daily
IV	10	1 700	0 653	0 865	1 518	+0 182	1 602	1 021	0 352	1 373	+0 229	Calcium lactate 3 0 grams daily Cod liver oil 24 0 cc. daily
V	10	2 115	0 614	1 096	1 710	+0 405	1 933	1 087	0 397	1 484	+0 449	Same as period IV plus Candiolin* 3 tablets daily
VI	10	2 601	0 623	1 405	2 028	+0 573	2 351	1 189	0 504	1 693	+0 658	Same as period IV plus Candiolin 6 tablets daily
VII	10	1 398	0 621	0 696	1 317	+0 081	1 648	1 082	0 318	1 400	+0 248	Same as period VI for first three days and then no medication
VIII	10	1 087	0 633	0 484	1 117	−0 030	1 477	1 051	0 285	1 336	+0 141	Strychnine sulfate 1 0 mgm. (grains 1/60) daily
IX	10	1 156	0 694	0 427	1 121	+0 035	1 522	1 097	0 272	1 369	+0 153	Thyroid extract 0 13 gram (grains II) daily
X	10	1 119	0 868	0 612	1 480	−0 361	1 530	1 103	0 324	1 427	+0 103	Thyroid extract 0.2 gram (grains III) daily Whole pituitary gland 0.2 gram (grains III) daily
XI	12	1 125	0 842	0 761	1 603	−0 478	1 501	1 066	0 278	1 344	+0 157	Same as period X for 2 days and then no medication
XII	16	1 133	0 746	0 554	1 300	−0 167	1 790	1 139	0 319	1 458	+0 332	Quartz lamp therapy Eleven treatments
XIII	8	1 185	0 780	0 451	1 231	−0 046	1 966	1 353	0 365	1 718	+0 248	No medication
XIV	13	1 362	0 856	0 510	1 366	−0 004	2 044	1 316	0 369	1 685	+0 359	No medication

* Candiolin contains by analysis 0 17 gram of calcium and 0 14 gram of phosphorus per tablet.

The roentgenograms of November 4, 1926 revealed thinning of the cortex of the long bones, healed recent oblique fracture of lower end of the right humerus in good position and an old healed fracture of the upper third of the left ulna with slight deformity The skull revealed numerous decalcified areas A large cyst in the right femur described during his previous admission was somewhat smaller The dorsolumbar spine showed diminution of the width of the vertebrae with pressure atrophy and slight kyphosis When these plates were compared with plates taken ten months previous there seemed to be some increased density of the bones On April 27, 1927 the osseous system was the same as described on November 4, 1926

EXPERIMENTAL RESULTS

The changes, which occurred in the calcium and phosphorus balances and the medicines given are presented in table 1 The studies cover 14 consecutive periods between November 15, 1926 and April 17, 1927 The results are reported as the average daily intake and output for each period The methods applied to these studies were the same as used for our previous observations (1)

During the first period he received approximately 1 0 gram of calcium per day and both the calcium and phosphorus were constituents of the foods eaten This period was obtained as a comparison with previous studies reported in Paper I (1) It revealed a definite positive balance for both calcium and phosphorus The positive calcium balance was explained by the unusually small amount of calcium excreted in the feces, which is much lower than any other observations on this subject

In period II he received subcutaneous injections of surgical pituitrin, 0 5 cc twice daily, for 6 days during the first half of the period He remained in positive calcium balance but a definite increase in the calcium in the feces was noted

In period III, 3 grams of calcium lactate which contained 0 4 gram of calcium were added to the diet daily without any increase in calcium retention No change in phosphorus intake was made There was a definite increase in the calcium excreted in both urine and feces

In the next period cod liver oil, 24 cc per day was added to the diet One cubic centimeter of the cod liver oil contained by analysis 0 002

increased ranging between 90 and 110 per minute showing a definite thyroid effect

The thyroid and pituitary medications were continued in period XI for two days and then stopped because of further increase in pulse rate of 110 to 115 per minute and discomfort on the part of the patient During the remainder of the period no medication was given A marked negative calcium balance was obtained with no particular

TABLE 2

Serum calcium and phosphorus determinations

Date	Calcium	Phosphorus
1926	*mgm. per 100 cc.*	*mgm. per 100 cc.*
November 9	14 8	2 0
November 16		2 2
November 26	14 0	2 8
November 29	14 4	2 9
December 3	13 3	2 9
December 17	15 4	2 9
1927		
January 5	14 2	2 5
January 17	11 3	2 8
January 19	12 0	2 1
January 25	14 0	2 8
January 31	12 5	2 8
February 8	13 5	2 8
February 21	14 6	3 0
March 7	14 8	2 9
March 21	14 9	2 6
March 28	14 4	2 6
April 4	14 4	2 5
April 18	14 1	2 6
Average all determinations	13 9	2 6

change in the amount of the phosphorus retained The pulse during the last half of the period varied from 80 to 100 per minute.

Quartz lamp therapy was applied in period XII He received 11 treatments applied both to front and back The calcium intake averaged 1 1 gram per day and phosphorus 1 8 gram The calcium in the urine and feces and the negative calcium balance diminished either due to the light therapy or to a wearing off of the thyroid effect

gram of calcium and 0 036 gram of phosphorus The calcium lactate was continued He received 1 7 gram of calcium and 1 6 gram of phosphorus daily The retention of calcium and phosphorus was greater in spite of increased excretion of both in the feces

During periods V and VI the intakes of calcium and phosphorus were increased by adding, to the combination given in period IV, candiolin, first 3 tablets daily and then 6 tablets in period VI Candiolin[2] (calcium hexose phosphate) was given with the hope that the calcium and phosphorus in combination with the hexose might be more easily absorbed and stored 0 57 gram of calcium and 0 66 gram of phosphorus were retained daily in period VI In each period there was again an increased excretion of both minerals in the feces with no definite increase in the urine

The intake of period VI was continued for 3 days in period VII and then all medications were stopped This change resulted in sharp drop in calcium and phosphorus retained as well as the amounts excreted in the feces

Period VIII duplicated period I as far as calcium intake was concerned but there was a slightly greater phosphorus intake The patient was just in calcium balance but had good positive phosphorus balance He excreted 0 48 gram of calcium daily in the feces as compared with 0 06 gram in period I which accounts for the difference in calcium retained

Thyroid extract 0 13 gram (2 grains) daily was given by mouth during period IX The intakes and balances remained practically the same as during period VIII but there was a tendency for the urinary calcium to climb The pulse varied between 70 and 90 during this period showing no evidence of thyroid intoxication

In period X the thyroid extract was increased to 0 2 gram (3 grains) and in addition whole pituitary gland extract, 0 2 gram (3 grains), was given by mouth Here a daily negative calcium balance of 0 36 gram was found with a slight drop in the positive phosphorus balance There was an increase of calcium in both urine and feces The pulse

[2] The candiolin used was obtained through the kindness of the Winthrop Chemical Company, New York City Each tablet contained by analysis 0 17 gram of calcium and 0 14 gram of phosphorus

mgm lower and the phosphorus 0 5 mgm higher during the second period of observation

The basal metabolism observations made in the Sage calorimeter are shown in table 3 The first two observations were made during the first period of study before the removal of the two parathyroid bodies and the others during the second admission after the removal of these parathyroid bodies In observation I the patient had difficulty in getting into a completely comfortable position and consequently was somewhat restless The fifth observation was made after the first week on thyroid extract and shows only a slight increase of metabolism over the previous observation The last test was made at the end of his thyroid and whole pituitary period and here is seen an increase in his metabolism which is, however, well within the normal variations At the time of this observation his pulse ranged between 110 and 115 per minute which would suggest a greater degree of thyroid intoxication than the metabolism test indicated

DISCUSSION

Relation of calcium intake to calcium retention A diet, containing 1 0 gram of calcium as calcium, was needed to prevent its loss from the body of this subject This fact has been demonstrated before both from his previous studies in this clinic (1) and from subsequent studies by Bauer, Albright, and Aub (2) In making up a high calcium diet one turns to milk and cheese as two of the main sources It is difficult to make up a palatable diet with much more than 1 0 gram of calcium per day It was because of this fact that calcium lactate and candiolin were added When the calcium in the diet was increased by the use of these medications a definite retention was observed as in periods V and VI The retention did not bear a quantitative relation to the intake, for an increase of 1 2 gram in the daily calcium, between periods III and VI, only resulted in an increased retention of 0.5 gram The remainder of the extra calcium intake, 0 7 gram daily, was excreted in the feces This suggests that only about 40 per cent of the extra calcium ingested, was absorbed

The effect of glandular extracts The use of pituitrin in period II resulted in a sharp drop in the amount of calcium retained This change was due entirely to the increased excretion of calcium in the

His pulse was at its normal level during this period The positive phosphorus balance was definitely increased

In periods XIII and XIV his intake of calcium was approximately 1 3 gram and his phosphorus 2 0 grams daily He received no supplementary medications He remained practically in calcium balance with a good positive phosphorus balance In these periods the intake

TABLE 3

Observations on the basal metabolism of C M made in the Sage calorimeter 1926–27

Number	Date	Weight	Height	Surface area by chart	Calories* per hour	Calories per square meter per hour	Variation† from Aub Du Bois Standards	Remarks
	1926	*kgm*	*cm*	*square meters*	*calories*	*calories*	*per cent*	
1	March 5	65 3	168	1 73	63 2	36 5	−7 6	Slightly uncomfortable and restless
2	March 26	65 1	168	1 73	57 2	33 1	−16 3	Two parathyroid bodies removed
3	November 11	69 0	168	1 80	59 7	33 2	−16 2	
	1927							
4	January 12	72 0	168	1 82	65 0	35 7	−9 6	
5	February 16	74 1	169	1 85	67 2	36 3	−8 1	0 13 gram thyroid extract daily for 8 days
6	March 2	74 0	169	1 85	69 5	37 6	−4 8	Thyroid extract 0 2 gram and whole pituitary extract 0 2 gram for 10 days—pulse 100–110

* The calories per hour are the average of three consecutive hours in the calorimeter

† The normal calories per square meter per hour by Aub-Du Bois standards are 39 5

of phosphorus was increased to see if it might not favorably influence the calcium retention

The results of 18 determinations of the serum calcium and phosphorus are presented in table 2 The average serum calcium was 13 9 mgm per 100 cc and the average serum phosphorus was 2 6 The averages for 9 determinations reported in Paper I (1) and made before the removal of two parathyroid bodies were calcium 15 3 mgm per 100 cc and phosphorus 2 1 mgm The serum calcium was 1 4

mgm lower and the phosphorus 0 5 mgm higher during the second period of observation

The basal metabolism observations made in the Sage calorimeter are shown in table 3 The first two observations were made during the first period of study before the removal of the two parathyroid bodies and the others during the second admission after the removal of these parathyroid bodies In observation I the patient had difficulty in getting into a completely comfortable position and consequently was somewhat restless The fifth observation was made after the first week on thyroid extract and shows only a slight increase of metabolism over the previous observation The last test was made at the end of his thyroid and whole pituitary period and here is seen an increase in his metabolism which is, however, well within the normal variations At the time of this observation his pulse ranged between 110 and 115 per minute which would suggest a greater degree of thyroid intoxication than the metabolism test indicated

DISCUSSION

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The effect of glandular extracts The use of pituitrin in period II resulted in a sharp drop in the amount of calcium retained This change was due entirely to the increased excretion of calcium in the

feces, as no change in amount excreted in the urine was noted The use of whole pituitary gland extract in period X was associated with the administration of thyroid extract so its individual effect was not observed

Thyroid extract was given during periods IX and X In period IX no appreciable change in the calcium balance was noted There was a slight increase in the calcium excreted in the urine In period X when the physiological response to the thyroid was observed in pulse and basal metabolic rate, there was definite swing of the calcium balance to the negative side An increased excretion of calcium was found in both urine and feces These results may be produced by thyroid extract alone as has been shown by Aub and his collaborators (3) in studying the excretion of calcium in thyrotoxicosis While it is impossible to demonstrate from these studies which one of the two glandular substances produced the results obtained, the use of the two resulted in definite reduction in amount of calcium retained even to the extent of producing a negative calcium balance There is suggestive evidence that pituitary extract may have increased the excretion of calcium in the feces while thyroid extract increased the excretion in the urine

The excretion of calcium in urine and feces The excretion of calcium in the urine remained uniform from period III to VIII but showed a definite increase during the glandular medication in periods IX and X This increase persisted through the remainder of the observations The amount of calcium found in the feces was closely related to intake With the increasing amount of calcium ingested there occurred a corresponding increase of calcium in the feces which represented approximately 50 to 60 per cent of the increase in the calcium taken The ratio between the amount of calcium excreted in the urine and in the feces, in our previous studies (1) was found to be about 4 1 In our present observations it varied widely being dependent mostly on the amount of the calcium intake In period I the ratio was 9 1 and in period VI it was, 1 2 2 The average ratio for the entire period was approximately 1 1 In comparing these findings with our previous observations, it must be noted that the intake of calcium during the later studies was continuously above 1 0 gram while in the earlier studies it was 1 0 gram or less

Relation of phosphorus intake to phosphorus and calcium retention The average phosphorus intake for the first three periods was 1 3 gram per day and he showed slightly positive balances on this intake The intake was increased during periods IV, V, and VI and the greatest retention was obtained with an intake of 2 4 gram daily The excretion and retention of phosphorus was not affected by administration of thyroid or pituitary extracts

The calcium retention did not appear to be affected by the levels of the phosphorus intake The greatest retention of calcium was obtained in period VI and coincided with the greatest retention of phosphorus Also in the last two periods where the intake of calcium was one half of the intake of period VI and the intake of phosphorus was nearly the same we found slightly negative calcium balances in spite of good positive phosphorus balances

The effect of removal of two parathyroid bodies on the level of serum calcium and phosphorus and on the basal metabolic rate In comparing the determinations of serum calcium and phosphorus during the present studies with those of our earlier studies (1) it was found that the average serum calcium was 1 4 mgm lower and the serum phosphorus 0 5 mgm. higher during the second period of study after two parathyroid bodies had been removed These findings suggest that a slight benefit occurred as a result of removing two parathyroid bodies but the changes are so small that they cannot be considered conclusive especially since a greater intake of calcium and phosphorus was maintained during the second period of observation

No change was observed in the basal metabolic rate as a result of the parathyroidectomies It was naturally increased somewhat as a result of thyroid administration

SUMMARY AND CONCLUSIONS

1 Calcium and phosphorus balances are presented for the subject C M who was observed continuously for 154 days

2 Distinct improvement in patient's physical condition occurred during his stay in the hospital

3 An intake of 1 0 gram of calcium was found necessary to keep him in positive calcium balance The positive balance was increased by increasing the intake No definite benefit could be ascribed to cod

liver oil or quartz lamp therapy Thyroid and pituitary extracts diminished the amount of calcium retained

4 The excretion of calcium in the urine was not affected by increased intake of calcium but was increased as a result of giving thyroid extract The excretion of calcium in the feces was elevated by increasing the intake and there is suggestive evidence that it is slightly increased by giving pituitary extracts

5 The excretion of phosphorus in the urine was not significantly affected by either intake or glandular therapy The phosphorus in the feces varied with the intake

6 A positive phosphorus balance was maintained throughout the entire period of observation even in those periods when there was definite loss of calcium from the body

7 The removal of two parathyroid glands caused only slight changes in the levels of serum calcium and phosphorus and no change in the basal metabolic rate

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STUDIES IN CONGESTIVE HEART FAILURE

I The Effect of Edema on Oxygen Utilization

By TINSLEY RANDOLPH HARRISON and COBB PILCHER

(From the Department of Medicine Vanderbilt University School of Medicine)

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The cardinal symptoms of heart disease are dyspnea, edema, and pain The recent important publication of Keefer and Resnik (1928) has done much to remove the subject of cardiac pain from the realm of controversy, and to lead to a better understanding of the mechanism by which it is produced, and hence, to a clearer clinical concept of its significance Unlike cardiac pain, edema and dyspnea are ordinarily indications of congestive heart failure and although these two symptoms have been the subject of many valuable studies there is not yet entire agreement as to the exact physiological disturbances which lead to their production

The observations to be presented in this paper are the first of a series of investigations devoted to the subject of heart failure Therefore, it seems appropriate to mention briefly the various modern theories as to the mechanism by which the important symptoms are produced

1 Inadequate cardiac output According to this conception, all the symptoms of heart disease are to be explained by the inadequacy in the amount of blood pumped by the heart (Mackenzie, 1925) This hypothesis has been widely accepted in English-speaking countries Thus "The efficiency of the heart is nothing else than the volume of blood that it can pump in relation to the oxygen requirement of the body This applies to the athlete, the man of sedentary habits, and to the cardiac patient The index of efficiency is therefore the arteriovenous difference during rest and varying degrees of muscular exertion" (Henderson Haggard and Dolley, 1927) Similarly, Meakins and Long (1927) state "Circulatory failure may be defined as a state in which the volume of blood circulated per unit of time is not adequate for the physical needs of the moment." The proponents of the 'inadequate cardiac output" theory have usually not stated just how the inadequacy produces edema Increased capillary permeability has been suggested but has not been clearly demonstrated until recently when Landis (1928) showed that anoxemia did tend to make fluid pass out of the capillaries more readily Martin Fischer (1921) believed that diminished blood flow led to the accumula

tion of acid in the tissue cells, thereby increasing their water-binding power, and he attributed cardiac edema to this cause

2 Slowing of the circulation Plesch (1926) reported prolonged circulation time, increased blood volume and increased minute output in heart disease (*"Bei Herzkranken ist im allgemeinen das Minutenvolumen erhöht"*) He showed that the circulation time is prolonged and believed that this led to increased permeability of the capillary walls, which caused edema Blumgart and Weiss (1927) observed diminished velocity of blood flow in cardiac decompensation They did not conclude definitely, however, that this was the essential cause of the edema

3 "Back-pressure" In Germany and in France many observers seem to believe that the symptoms of heart failure are essentially dependent on a damming of blood in, and back from, a dilated heart Krehl (1917) may be cited as one of the leading advocates of this view Vaquez (1924) distinguishes sharply between left and right ventricular failure and, like Krehl, regards pulmonary congestion as secondary to the former and peripheral congestion to the latter In each instance he seems to consider "back-pressure" as the essential factor This is different from the conception of Mackenzie who regarded pulmonary edema as due to inability of the "enfeebled" right ventricle to pump blood through the lungs, and considered peripheral congestion and edema as due to similar failure of the left ventricle

4 Lack of balance between the ventricles This is essentially a modification of the "back-pressure" theory, in as much as the ventricle which is working under the greatest handicap is considered as failing to keep pace in output with the other less hampered ventricle and consequently congestion as occurring "back" of the failing side of the heart This concept was applied to cardiac asthma by Eppinger, von Papp, and Schwarz (1924) Robinson (1927) and Harrison and Leonard (1926) have attempted to explain other circulatory phenomena of heart failure on this basis

5 A combination of the above-mentioned theories Certain authors believe that different patients present different types of circulatory derangement Thus, Burwell (1928) believed that dyspnea on exertion in compensated cardiacs might be due to relative inability to increase the cardiac output, whereas edema could be explained by lack of ventricular balance

Wiggers (1925) has compared cardiac failure in man to the conditions in animals poisoned by chloroform or other drugs which "depress" the heart He believed that "back-pressure," when it occurred was secondary to decreased output due to myocardial weakness Gibson (1927) believed that both diminished output and "back-pressure" were causative factors in the production of edema

6 Disturbances of lactic acid metabolism. In 1927 Eppinger, Kisch and Schwarz published a monograph in which a new point of view was stated and very important data were presented concerning heart failure These authors do not believe that cardiac failure can be explained by hemo-dynamics alone Briefly summarized, their theory is that there is a disturbance in the resynthesis of lactic acid in heart disease More than the usual one-fifth of the lactic acid produced has to be

burned to accomplish which, oxygen consumption at rest and during exercise would have to be increased When such compensation is inadequate the accumulation of lactic acid in the tissues leads to diminished buffering power At first, the carbon dioxide tension of the blood is increased and this causes cardiac dilatation and increased output. Later, due to the excessive loss of bicarbonate, a state of acapnia supervenes and this causes slowing of the circulation, with diminished output, which produces edema and cyanosis More recently Eppinger, Laszlo, and Schürmeyer (1928) have found that in animals in a state of shock, and with diminution of the circulating blood volume, the oxygen requirement for a given amount of work is increased. They believe that in congestive heart failure the circulating blood volume is similarly decreased because of the stagnation of large portions of the blood in various depots of the body The circulation through the muscle is therefore diminished as in acute circulatory collapse, and the state of oxygen lack thereby produced leads to the abnormal chemical processes in the muscles

This short summary states the main points in each of the more important hypotheses of cardiac failure Without a more detailed discussion, it is sufficient here to point out that the currency of so many theories suggests the need for further work.

It has seemed to us that a study of the symptoms of the cardiac patient offered the best approach to the problem Consequently, this and succeeding papers to appear at an early date are concerned with cardiac edema In the present publication our observations concerning the effect of edema on the circulation are presented

METHOD

If one assumes constancy of oxygen consumption in a given portion of the body, then the more blood which flows through it per minute the less will be the amount of oxygen removed from each unit of blood Likewise, when blood flow is decreased the amount of oxygen taken out per unit of blood will be correspondingly increased Therefore, the oxygen utilization or arteriovenous difference of blood from given vessels affords, subject to the assumption mentioned, a general index to the amount of blood passing through the corresponding portion of the body

Other investigators have studied the arteriovenous difference in the arms of patients suffering from cardiac disease Lundsgaard (1918) observed increased utilization in all individuals with congestive failure and in "compensated" patients when the rhythm was markedly irregular Harrop (1919) found that the arteriovenous oxygen differ-

ence of blood drawn from the arm was usually greater when failure was present than when it was absent On the other hand, Eppinger, von Papp, and Schwarz (1924) frequently found normal or low values for oxygen utilization in their patients with congestive failure

Instead of using blood from an arm vein we have studied the blood from the the femoral vein The arms are rarely edematous in cardiac failure, the legs usually are Hence, the state of the blood drawn from the legs may be expected to be a better index of the blood flow through edematous tissues The only previous studies on the femoral venous oxygen are those of Blalock (1929) who found low utilization in patients with varicose veins His results were rather surprising and led us to undertake a similar study in patients with heart disease

Our observations were made after the patient had been lying quietly for twenty minutes or more in a semi-recumbent posture This position was necessary because the subjects were often too short of breath to lie flat and because femoral venepuncture is difficult when the subject is sitting upright The skin was sterilized in the usual manner, the femoral arterial pulsation felt and the puncture made at a point about three centimeters below Poupart's ligament and one centimeter medial to the point of maximal arterial pulsation The needle was inserted vertically for a distance of two to five centimeters, depending on the size of the patient and the amount of fat With a little practice the procedure was found to be easily carried out The patients complained of no more pain than from an ordinary venepuncture

The blood was drawn into a syringe containing oil and immediately expelled into a one-ounce bottle containing a small amount of oxalate and 10 cc of oil Oxygen determinations were made in duplicate on the Van Slyke-Neill (1924) manometric apparatus In most instances analyses for carbon dioxide content were made also

Arterial blood was drawn in the usual manner from the brachial or from the femoral artery

A few observations were made on individuals with no disease of the heart or blood vessels, and a number of patients with edema due to some cause other than heart disease were studied The cardiac patients represented all grades of congestive failure In most instances the same patient was investigated with various degrees of edema

The degree of edema of the legs has been judged according to the extent of distribution The term "marked edema" has been used to describe those cases in which the entire lower extremity was involved When the entire leg below the knee was swollen but the thighs were not, the cases were considered to have "moderate" edema Edema confined to the ankles and feet has been called "slight" Since the presence of edema in a given spot had to be determined by "pitting," and since it is well known that a leg may contain a liter or more of excess fluid without demonstrable "pitting," it is obvious that what we have called "no edema" was really, in some instances, unrecognized edema.

It soon developed from our studies that digitalis intoxication had a marked effect on the femoral venous oxygen content. Therefore, it became necessary to adopt certain definite criteria for classifying our patients in this regard Accordingly, any individual who had been receiving digitalis was considered to be suffering from over-dosage whenever he developed (*a*) nausea, (*b*) vomiting, or (*c*) pulsus bigeminus, provided that the toxic symptoms disappeared within three days after the administration of the drug was stopped

Diminished alkali reserve of the blood was also found to be frequently associated with unusual changes in the oxygen utilization It became necessary, therefore, in analysing our results to fix an arbitrary level below which our patients would be considered as acidotic We have classified all individuals with an arterial carbon dioxide content of forty volumes per cent or less as having acidosis In a few instances the arterial carbon dioxide content was not determined and in such cases, normal values have been assumed

The patients studied were all adult males Two of them had congestive heart failure caused by syphilitic aortic insufficiency The others had congestive failure without valve lesions (During the six months in which these studies were carried out we have not had a single adult male with congestive heart failure of rheumatic origin in the Vanderbilt University Hospital This illustrates the rarity of rheumatic heart disease in the southern states as compared with other parts of the country (Harrison and Levine, 1924))

Some of the cardiac patients had regular rhythm, others had auricular fibrillation, and a third group had ectopic beats

RESULTS

The *oxygen capacity* exhibited no constant change, as the edema disappeared, in those individuals who had had edema for a long time However, two of our patients (McC and G C) had been edematous for only a few days when they came to the hospital In those individuals diuresis was accompanied by a sharp rise in oxygen capacity In their cases true hydremia (i e , edema of the blood stream) seems to have been present In two patients (C H and M E) who suffered from chronic pulmonary infections, a gradual slight fall in oxygen capacity was noted during several months of observations Presumably, this anemia was due to the infectious process

The *arterial saturation* was usually within normal limits or only slightly abnormal Patients who had chronic pulmonary disease, acute severe pulmonary edema or acute pneumonia had low arterial saturations The lowest value which we found was 47 5 per cent in (H C) dying of acute bronchopneumonia superimposed upon a rather severe degree of pulmonary edema In one patient with uncomplicated pulmonary edema, an arterial saturation of 79 per cent was found twenty hours before death

Our most striking instance of arterial anoxemia occurred, however, in a man (M E) with chronic bronchitis, atelectasis and bronchiectasis of extreme degree This case will be reported elsewhere in detail It is sufficient to state here that he lived for a period of several months with an arterial saturation below 75 per cent, and that he lived at least one month with his arterial blood less than 60 per cent saturated

In general, it may be said that severe arterial anoxemia in patients with acquired cardiac disease occurs only in the presence of (*a*) acute or chronic pulmonary infection or (*b*) severe pulmonary edema Slight degrees of anoxemia are common in patients with senile emphysema or moderate congestion and edema of the lungs Many patients who have marked pulmonary congestion, as revealed by their vital capacities, accompanied or not by slight or moderate pulmonary edema, as judged by râles over the bases of the lungs, have arterial saturations within normal limits These conclusions are similar to those arrived at by Meakins (1923) and by Eppinger, Kisch and Schwarz (1927)

The femoral venous oxygen content and the oxygen utilization of the legs As our findings in this connection appear to be new and not with-

out significance they will be presented in some detail In table 1 are shown the results of twelve analyses of blood from the femoral veins of several hospital patients who were selected at random and who had no edema and no disease of the heart or blood vessels The

TABLE 1

The resting oxygen utilization of individuals with no disease of the circulatory system and no edema

Subject	Arterial oxygen content	Femoral venous oxygen content		Arteriovenous difference		Oxygen capacity	Percentage arterial saturation	Arterial carbon dioxide content	Remarks
		Right	Left	Right	Left				
	volumes per cent	volumes per cent	volumes per cent	volumes per cent	volumes per cent	volumes per cent		volumes per cent	
B M.	12 96	6 18	6 67	6 78	6 29	14 40	92 0	45 4	Convalescent from repair of inguinal hernia
H R.	15 45	6 81		8 64		18 77	84 1	42 5	During mild attack of bronchial asthma
T F	13 80	7 09		6 71		15 30	92 9	42 5	Carcinoma of stomach
G T	17 45	6 89	8 00	10 56	9 45	18 95	94 2	41 2	Balanitis (temperature 39 8°C.)
N S	15 92	3 26	5 92	12 66	10 00	17 24	94 5	45 2	Injury of eye
C. A.	15 30	7 00	11 03	8 30	4 27	17 08	91 6	44 2	Amebic dysentery
D S	14 60	9 72	10 55	4 88	4 05	16 00	93 3	42 2	Convalescent from suprapubic cystostomy
F R.	14 61	9 14		5 47		16 80	89 1	41 9	Peptic ulcer
C. L	12 00	9 03		2 97		13 80	89 2	47 8	Lung abscess
J W	14 71	12 21		2 50		15 80	95 2	41 1	Diabetes mellitus

Lowest arteriovenous difference 2 50 Highest arteriovenous difference 12.66 Average arteriovenous difference 6.90

highest, lowest and average arteriovenous differences were 12 66, 2.50 and 6 90 volumes per cent, respectively

Similar studies on patients with marked edema due to congestive heart failure are depicted in table 2 The highest, lowest and average utilization values in sixteen observations on seven patients were 9 00, 1 26 and 4 08 volumes per cent, respectively

In table 3 are shown the studies on five individuals with moderate edema In these eleven observations the figures for utilization vary

TABLE 2

The resting oxygen utilization of individuals with cardiac disease and marked edema*

Subject	Date	Arterial oxygen content	Femoral venous oxygen content		Arteriovenous difference		Oxygen capacity	Percentage arterial saturation	Arterial carbon dioxide content	Remarks
			Right	Left	Right	Left				
		volumes per cent	*volumes per cent*	*volumes per cent*	*volumes per cent*	*volumes per cent*	*volumes per cent*		*volumes per cent*	
McC	August 13, 1928	15 95	9 93	10 64	6 02	5 31	17 25	94 5	43 5	White, male, 72, hypertension, arteriosclerosis, regular rhythm
G C	September 8, 1928	12 22	10 90	10 96	1 32	1 26	14 00	87 4	45 7	Negro, male, hypertension, arteriosclerosis, regular rhythm
C H	July 21, 1928	13 08	8 53	9 66	4 55	3 42	14 25	93 8		White, male, 42, syphilitic aortic insufficiency, empyema, regular rhythm
	July 24, 1928	12 96	10 42	9 89	2 52	3 07	13 79	95 9		
H C	August 5, 1928	13 66	10 39	11 10	3 27	2 56	17 18	81 6	61 4	Negro, male, syphilitic aortic insufficiency, acute broncho-pneumonia, regular rhythm
R. P	August 2, 1928	17 45	13 68	14 85	3 77	2 60	18 16	98 1	42 9	White, male, 58, hypertension, arteriosclerosis, auricular fibrillation
M E	September 5, 1928	12 30		8 55		3 75	20 00	63 5	58 5	White, male, 42, bronchiectasis, atelectasis, regular
T B	November 23, 1928	17 80	12 30		5 50		19 26	94 5	45 8	Negro, male, 74, hypertension, arteriosclerosis, auricular fibrillation
	November 25, 1928	17 52		10 16		7 36	19 33	92 6	47 9	
	November 28, 1928	17 18	8 18		9 00		18 28	96 0	41 0	

Lowest arteriovenous difference 1 26 Highest arteriovenous difference 9 00 Average arteriovenous difference 4 08

* Patients with "pitting" of the entire leg and thigh have been classified as having marked edema

TABLE 3

The resting oxygen utilization of individuals with cardiac disease and moderate edema*

Subject	Date	Arterial oxygen content	Femoral venous oxygen content		Arteriovenous difference		Oxygen capacity	Percentage arterial saturation	Arterial carbon dioxide content	Remarks
			Right	Left	Right	Left				
		volumes per cent	*volumes per cent*	*volumes per cent*	*volumes per cent*	*volumes per cent*	*volumes per cent*		*volumes per cent*	
F H.	December 15, 1928	14 55	10 42		4 13		16 25	91 6	48 6	Negro, male, 58 hypertension, arteriosclerosis, auricular fibrillation
C H.	July 29, 1928	13 00	8 44	7 37	4 56	5 63	13 79	96 3		See table 2
R. P	August 6, 1928	16 70	11 00	11 60	5 70	5 10	17 61	97 0	43 8	See table 2
	August 8 1928	15 75	10 64	11 00	5 11	4 75	16 31	98 6	40 4	
M E.	November 16, 1929	8 77		2 90		5 87	16 63	54 7		See table 2
	November 23, 1928	11 63		5 76		5 87	18 90	83 5	59 1	
J R.	August 30, 1928	13 65	7 78	9 62	5 87	4 03	14 00	99 5	52 0	White male, 57, hypertension, arteriosclerosis, numerous ectopic beats

Lowest arteriovenous difference 4.03 volumes per cent. Highest arteriovenous difference 5 87 volumes per cent. Average arteriovenous difference 5 15 volumes per cent.

* Patients with "pitting" of the entire leg below the knee but with very slight or no pitting of the thigh have been classified as having moderate edema.

TABLE 4

The resting oxygen utilization of individuals with cardiac disease and slight edema*

Subject	Date	Arterial oxygen content	Femoral venous oxygen content		Arteriovenous difference		Oxygen capacity	Percentage arterial saturation	Arterial carbon-dioxide content	Remarks
			Right	Left	Right	Left				
		volumes per cent	*volumes per cent*	*volumes per cent*	*volumes per cent*	*volumes per cent*	*volumes per cent*		*volumes per cent*	
A. A	February 2, 1929	13 73	4 80		8 93		14 70	95 4	42 1	White male, 35, hypertension, regular
M E	September 10, 1928	15 47		11 42		4 05	20 68	76 9	56 6	See tables 2 and 3
	November 27, 1928	12 44		4 71		7 73	18 05	70 9	57 2	
R P	August 13, 1928	16 80	12 88	13 12	3 92	3 68	17 70	97 0	42 4	See tables 2 and 3
	August 22, 1928	17 02	11 80	11 92	5 22	5 10	17 48	99 2	41 0	
C H	August 11, 1928	11 20	5 53	5 18	5 67	6 02	12 12	94 6	51 3	See tables 2 and 3
McC	August 17, 1928	18 54	10 57	12 35	7 97	6 19	19 58	96 7	45 2	See table 2
G C	September 12, 1928	14 86	12 48	14 03	2 38	0 83	17 57	86 7	41 3	See table 2
	September 14, 1928	15 05	10 15	11 33	4 90	3 72	16 82	91 5		
	September 19, 1928	15 19	9 60	10 82	5 59	4 37	17 14	90 7	45 7	
F H.	December 23, 1928	14 84	8 76	8 16	6 08	6 68	16 17	93 8	43 4	See table 3
	August 27, 1928	13 04	4 98		9 06		14 38	90 6	44 6	
T B	December 6, 1928	17 02	9 97		7 05		18 02	96 4	45 8	See table 2

Lowest arteriovenous difference 0 83 volumes per cent. Highest arteriovenous difference 8 93 volumes per cent. Average arteriovenous difference 5 44 volumes per cent

* Patients with pitting of the ankles and feet only have been classified as having slight edema.

TABLE 5

The resting oxygen utilization of individuals with cardiac disease and no edema*

Subject	Date	Arterial oxygen content	Femoral venous oxygen content		Arteriovenous difference		Oxygen capacity	Percent age arterial saturation	Arterial carbon dioxide content	Remarks
			Right	Left	Right	Left				
		volumes per cent	*volumes per cent*	*volumes per cent*	*volumes per cent*	*volumes per cent*	*volumes per cent*		*volumes per cent*	
J R.	September 6, 1928	15 56	8 34		7 22		16 40	97 0	45 3	See table 3
M E.	September 17 1928	16 24		10 78		5 46	20 60	80 9		See tables 2, 3 and 4
	October 2 1928	13 90		7 98		5 92	18 50	77 2		
R. P	September 8, 1927	16 90	10 30	9 11	6 60	7 79				See tables 2, 3 and 4
McC.	August 23, 1928	18 04	12 33	12 82	5 71	5 22	18 95	97 4	43 4	See tables 2 and 4
	August 30 1928	19 18	11 86	11 02	7 32	8 16	20 47	95 8	45 5	
	September 6, 1928	19 20	10 62	10 86	8 58	8 34	19 54	98 4	43 9	
G C.	September 29, 1928	15 11	9 84	10 20	5 27	4 91	16 66	92 8		See tables 2 and 4
F H.	September 29, 1928	14 04	8 32	8 44	5 72	5 60	14 49	97 0	42 6	See tables 3 and 4

Lowest arteriovenous difference 4.91 Highest arteriovenous difference 8.58 Average arteriovenous difference 6 52

* No edema, as here used, means no pitting.

between 4 03 and 5 87 with an average value of 5 15 volumes per cent Similarly, in eight patients with slight edema, twenty-one observations, table 4, showed values of 0 83 to 8 93 volumes per cent with an average of 5 44 Six cardiac patients who had previously had edema

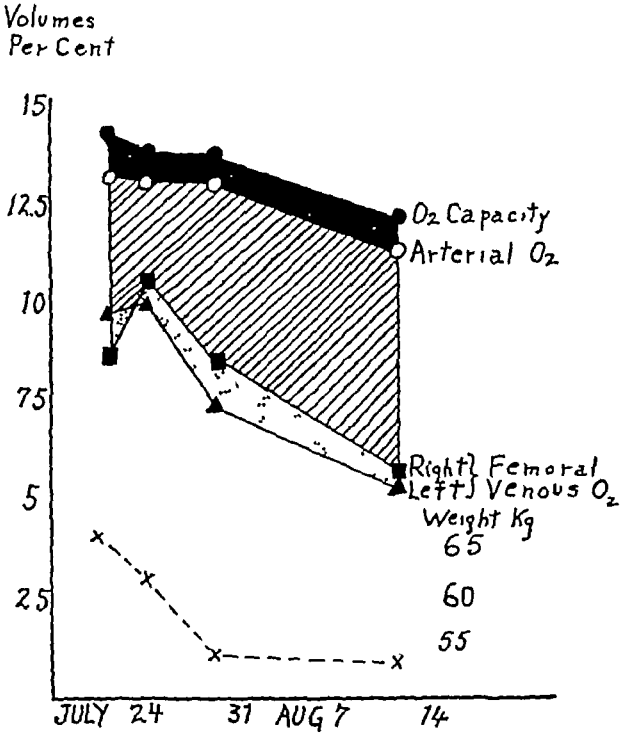

FIG 1 SUBJECT C H

As the edema diminished the utilization (shaded and dotted areas) increased The arterial oxygen saturation was within normal limits The oxygen capacity did not rise as edema diminished The edema had been present for more than six months

but who had no perceptible edema at the time the blood samples were drawn, were found in fifteen observations to have femoral utilizations of 4 91 to 8 58 with an average of 6 52 volumes per cent (table 5)

In figures 1, 2, and 3, individual patients have been charted In each individual the utilization was low when edema was present and rose as edema disappeared

The type of heart disease made no difference in the results The two patients with syphilitic aortic insufficiency and the patient with heart failure secondary to bronchiectasis reacted in the same way as did the larger group of individuals with hypertensive heart disease Patients who had auricular fibrillation showed the same changes as did those with sino auricular rhythm

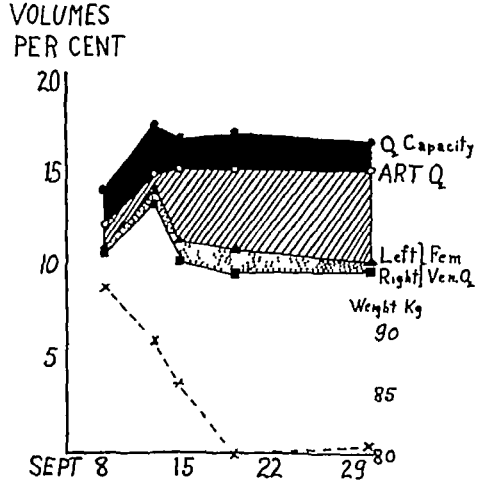

FIG 2 SUBJECT G C

As edema diminished the utilization increased The utilization, when he was edema free, was approximately four times as great as when he had marked edema He had had edema for only two weeks when he entered the hospital Improvement was associated with a sharp rise in oxygen capacity The arterial saturation was slightly subnormal

As a general rule, then, it may be stated that patients with hypertensive or syphilitic heart disease as well as patients with cardiac failure secondary to chronic pulmonary disease usually have, when edema of the legs is present, a high venous oxygen and a low femoral arteriovenous difference (utilization) The degree of diminution in oxygen utilization is roughly proportional to the amount of the edema

There are, however, at least two important exceptions to these generalizations One of these is seen in patients with digitalis intoxication and the other can be noted in individuals who are in a state of acidosis In table 6, data from patients who were suffering from

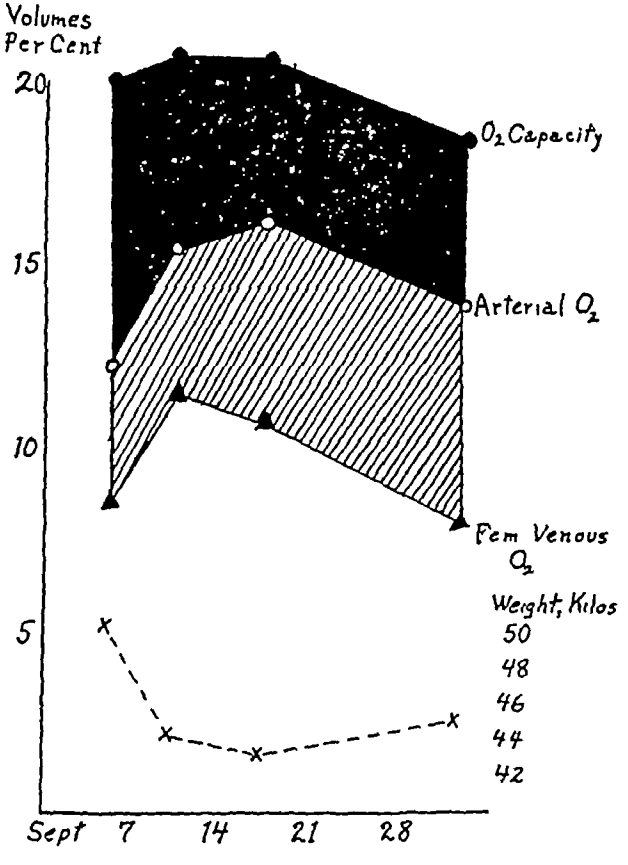

FIG 3 SUBJECT M E

As edema diminished the utilization increased The arterial saturation was very low The patient had bronchiectasis and atelectasis

digitalis over-dosage are presented It will be noted that regardless of the amount of edema, such patients have femoral venous oxygen contents which are lower and femoral oxygen utilizations which are higher than those seen in any of the groups which have been considered The values for utilization are even higher than those found

in control individuals In six observations on four patients the figures for lowest, highest and average arteriovenous oxygen differences were 6 10, 11 1 and 9 12 volumes per cent, respectively

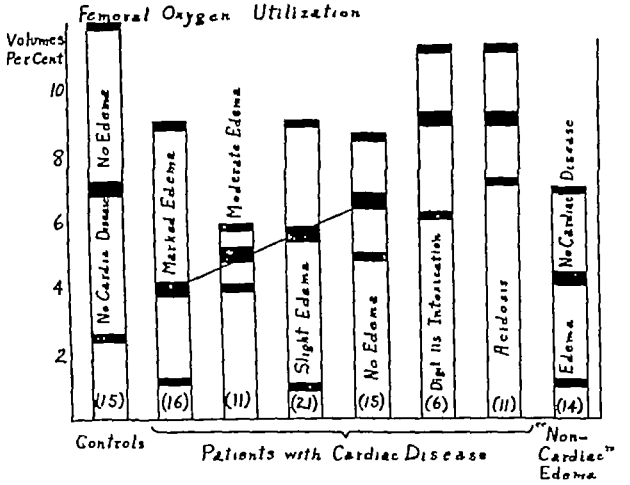

FIG 4

In each column the highest and lowest narrow bars indicate the highest and low est utilization, respectively The broader middle bars represent the average utilizations for the group It can be noted that subjects within each group show rather marked variations in utilization The average values are consistent, how ever The average utilization in the cardiac patients is almost an inverse linear function of the amount of edema The cardiac patients with no edema had uti lization values almost as high as did the control group The utilization was very high in patients with acidosis or digitalis intoxication The individuals with non cardiac edema had low arteriovenous differences, also, indicating that the diminu tion in utilization is not specifically associated with heart disease but is related to edema *per se* The figures in parentheses at the bottom of each column refer not to the number of patients in each group but to the number of observations of utilization.

In patients with acidosis (arterial CO 40 volumes per cent) similar findings were noted These are shown in table 7 Here the lowest